FIXATION OF UNCEMENTED IMPLANTS

By

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My thesis postulates that bone ingrowth and direct bone apposition combined with implants engineered to produce interfacial strains lead to beneficial bone remodelling which may result in fixation of joints that will last for the patients life-time.

The concept of extra-cortical plate fixation was investigated by assessing the bony response to plates of different design and surface coating. The study found that only one geometric design (holes) significantly increased bone ingrowth into the plate when compared with the control ($p=0.01$). A crystalline HA coating encouraged significantly greater interfacial contact when compared with a roughened titanium surface ($p=0.01$), a HA coating of lower crystallinity ($p=0.004$) and a solution precipitated HA coating ($p=0.02$). No significant differences were found when bone ingrowth into the plates were compared, except significantly more bone had grown into plates coated with a HA coating of lower crystallinity ($p=0.036$). Differences in bony reaction induced by the plates of different design were evident and therefore a combination of the correct design and surface coating are required for optimal bone attachment and ingrowth to extra-cortical plates.

An experimental goat model was developed to investigate hydroxyapatite coated extra-cortical plate fixation in massive segmental bone tumour replacements. On retrieval, all of the plates were securely fixed by new bone. Bone apposition had occurred through a combination of periosteal bone production, invasion of bone through slots and bone growth over the ends of the plate. It was concluded that due to both mechanical and biological effects, extra-cortical plate fixation generated new bone growth that enhanced fixation and encouraged plate integration into cortical bone.

The importance of the implant surface was demonstrated in a series of human autopsy retrieved hip implants. The proximal region of each implant was coated with either a plasma sprayed porous ingrowth surface (plain porous), a HA coated porous surface (porous HA) or a grit blasted surface.

Significantly more bone ingrowth ($p=0.012$) and bone attachment ($p<0.05$) was measured to the porous HA surface when compared with the plain porous surface. There was no significant difference in bone attachment between the plain porous and grit blasted surfaces.

A combination of a HA surface combined with extra-cortical plate fixation has been used to treat a number of bone tumour patients.

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I am privileged to work alongside some remarkable people and I acknowledge and am grateful for their contributions and support.

Deaconess E Pelham, thankyou for giving me strength in prayer and belief in myself. Jacqueline Pelham-Leigh and Jeremy Coathup - words alone are not enough. Thank you for being there.

Writing this thesis took years of hard work with many obstacles to conquer. It was only through faith and belief and His grace and mercy that it is now complete. *All things are done according to God's plan and decision.... based on what He had decided from the very beginning* (Eph. 1:11). *Happy are those who trust in the Lord....I could never speak of all the good things you have done* (Ps. 40:4-7). *Let us....praise Gods Glory* (Eph. 1:12).

This thesis is dedicated to my father for his love, strength and undying support .....Thanks Dad.

Chapter One

AN INTRODUCTION TO CEMENTED AND UNCEMENTED IMPLANT FIXATION

1.1 THE AIM OF THE DESIGN AND MANUFACTURE OF ORTHOPAEDIC IMPLANTS

The purpose of limb and joint preservation surgery is to eradicate disease, retain the integrity of the skeleton and preserve a limb with useful, pain-free function.

During the last century the treatment for malignant bone tumours was amputation (Rubin, 1971). This was because of poor results following attempts at local control of the tumour and the limited reconstructive techniques available (Sweetnam *et al.* 1971; Friedman and Carter, 1972). During the past 20 to 30 years a combination of early diagnosis of tumours, major advances in chemotherapeutic methods, radiation therapy (Jaffe and Knapp, 1983; Rosen and Marcove, 1983; Goodnight and Bargat, 1985; Rosen and Nirenburg, 1985; Springfield *et al.* 1988), and an understanding of the natural history and behaviour of these malignant tumours (Enneking *et al.* 1980; Simon, 1984; Watt, 1985; Sundaram and McGuire, 1986) have all increased the survival rate of bone tumour patients.

This has led to a renewed interest in limb-sparing procedures (Simon *et al.* 1986). The reconstructive options available to the surgeon include allografts (Mankin *et al.* 1987), arthodesis (Enneking and Shirley, 1977; Campanacci and Costa, 1979) or prosthetic replacement (Sim and Chao, 1979; Sim *et al.* 1987; Otis *et al.* 1989; Horowitz *et al.* 1991). Prosthetic replacement is generally considered an acceptable alternative to amputation (Simon *et al.* 1986; Abudu *et al.* 1996). The fixation of bone tumour implants to bone generally followed the fixation type used in standard total joint replacements.

In the early 1960's, Sir John Charnley developed the low friction arthroplasty. A combination of techniques including the use of PMMA, polymeric acetabular cups and rigorous attention to the prevention of infection ensured total hip replacement to become a successful procedure. The majority of patients who undergo THR are treated for osteoarthritis. Other indications for THR are

rheumatoid arthritis, particularly in the younger patient, osteonecrosis and trauma.

There is no acknowledged "best" material for the manufacture of orthopaedic implants (Ducheyne and Cohn, 1991; Galante *et al.* 1991; Black, 1992). Materials used can be grouped into three categories: metals, polymers and ceramics. The metals include commercially pure titanium, Ti-6Alwt%-4Vwt%, cobalt chrome-molybdenum alloy and 316L stainless steel. The polymers include ultra-high molecular weight polyethylene (UHMWPE) and polymethylmethacrylate (PMMA). The ceramics, such as alumina (Al_2O_3) and zirconia oxide demonstrate excellent biocompatibility and wear characteristics, although their brittleness and insufficient strength has limited their use. Calcium-phosphate ceramics such as hydroxyapatite have been shown to be biocompatible, non-toxic and capable of bonding directly to bone (Manley, 1993).

Cobalt-chrome alloy has low ductility but its most advantageous property is that of its extreme hardness that offers high wear resistance at the articulating surface (Friedman *et al.* 1993). The two most important additives to the cobalt base are chromium and carbon. The chromium is used to enhance corrosion resistance (due to the formation of passive chromic oxide), and the latter to improve the handling of the alloy (Weinstein and Clemow, 1990).

Titanium has played a significant role in numerous surgical procedures in the field of orthopaedics, cardiovascular and dental implantation. Titanium alloy Ti-6Al-4V is widely used in joint replacement. Its characteristics include low density, high tensile strength, resistance to fatigue, ductility, low modulus of elasticity, anti-corrosive properties (Rae, 1975; Solar *et al.* 1979; Kummer and Rose, 1983) and good biocompatibility (Albrektsson *et al.* 1981; Linter *et al.* 1986). In contrast, the known liabilities of titanium and its alloy include poor resistance to wear, notch sensitivity, and potential toxicity of aluminium and vanadium (McKellop *et al.* 1981; Buchanan *et al.* 1987; Agins *et al.* 1988;

McKellop and Clarke, 1988). It has also been reported that the titanium alloy is susceptible to abrasive wear by particles of acrylic cement (McKellop *et al.* 1981) and that titanium alloy with normal acid-passivated surfaces shows more damage to the surface and tends to generate more wear of polyethylene than comparable components made from stainless steel or cobalt-chromium (McKellop and Clarke, 1988; Agins *et al.* 1988; McKellop *et al.* 1990). Recent studies have improved the wear, corrosion and fatigue properties of titanium alloys by a process of ion implantation and titanium nitriding (Siohansi, 1976; Buchanan[a] *et al.* 1987; Williams and Buchanan, 1988).

The Young's modulus of titanium is 106 GPa and cobalt-chromium 230 GPa (Friedman *et al.* 1993). Both alloys are stiffer than cortical bone (25 GPa) (Dobbs and Scales, 1983). Titanium is a factor of two less stiff than cobalt-chromium. For this reason titanium produces less stress shielding and will deflect twice as much load to the bone than an identical structure made from cobalt-chrome (Johnson *et al.* 1979). Therefore, femoral stems and areas of bone-implant contact are usually made from titanium alloy. Fibre metal meshes and beads which are sometimes present on the implant surface are made from Ti (cp) because it is considered to be more biocompatible.

The polymers have some advantages over the metals. These include their low densities, lower cost, corrosion resistance, low modulus of elasticity, low fatigue characteristics, a low coefficient of friction, good solvent resistance and good processibility (Kabo, 1991). Ultra-high molecular weight polyethylene is used at the articular surface of acetabular and tibial components. The limitations of its mechanical properties have prevented its use as a load-bearing material (Mathys and Mathys, 1984).

There are several goals for the design and construction of major bone and joint prostheses. The implant must survive in the body without any negative tissue effects. It must permit the transfer of load onto the bone and it must remain stable and in place throughout the patients lifetime whether *in situ* for 1

year or 80 years. The mechanical, biological and design considerations involved in creating this implant are incredibly complex. Mechanically, implants in the normal active individual are subjected to fluctuating cyclic forces with oscillatory movements and are probably stressed between 1 million and 2.5 million times *per annum* (Wright, 1987). The magnitude and direction of these forces transmitted through a massive bone tumour prosthesis at any instant during various patient activities is largely unknown. The amount of bone and soft tissue resected is governed by the type and extent of the lesion. Therefore the function and movement and hence magnitude and direction of the forces transmitted by a massive bone tumour prosthesis are different in each patient.

1.2 CEMENT FIXATION AND ASEPTIC LOOSENING

Bone cement has been used extensively over the last 35 years and has proven to be successful in a variety of applications including denture fabrication, intraocular lenses, the repair of cranial defects and in the fixation of joint and bone tumour prostheses.

Current research into cement fixation generally aims at fine tuning the procedure and improving its mechanical and long-term performance properties. In terms of the restoration of normal daily activity and in the relief of pain, many follow-up studies of both total hip replacements and total knee replacements have reported excellent functional results following cemented fixation particularly for the older (> 65 years) patients (Kavanagh *et al.* 1989). In the younger, active and heavier patients concern was raised about a rapid increase in loosening of the components as the length of follow-up time increased (Beckenbaugh and Ilstrup, 1978; McBeath and Foltz, 1979; Stauffer, 1982; Sutherland *et al.* 1982; Coventry, 1981; Salvati *et al.* 1981; Schurman *et al.* 1989). It is estimated that more than 25% of all of the prosthetic implants inserted will shows signs of aseptic loosening and will require revision surgery (Stauffer, 1982; Glassman *et al.* 1993; Kim and Kim,

1993;). The most frequent long-term complication associated with cement fixation in all total joint and bone tumour replacements is aseptic loosening (Amstutz *et al.* 1976; Carlsson and Gentz, 1980; Unwin *et al.* 1995). Loosening can be attributed to numerous mechanical, material and biological factors that lead to resorption of bone adjacent to the cement (Berstrom *et al.* 1973; Mendes, 1973; Amstutz *et al.* 1976; Salvati *et al.* 1976; Nicholson, 1975; Reckling *et al.* 1977) with inevitable loss of fixation.

Many studies have reported gross loosening (Amstutz *et al.* 1976; Beckenbaugh and Ilstrup, 1978). They concluded that loosening was associated with a radiolucent line at the bone-cement interface (Berstrom *et al.* 1973; Weber and Charnley, 1975; DeLee and Charnley, 1979; Gruen *et al.* 1979) (however, this was not always a clinical indication of loosening (Reckling *et al.* 1977; Beckenbaugh and Ilstrup 1978; Carlsson *et al.* 1980)). Several theories have been developed to explain the initiation of a radiolucent line and subsequent loosening. These include failure to pack the cement tightly against the bone (Andersson *et al.* 1972), thermal necrosis with subsequent bone resorption resulting from the exothermic reaction accompanying polymerisation of the methylmethacrylate (Charnley[a], 1970; Slooff, 1971), and micromotion at the bone-cement interface. This results in the formation of a layer of condensed bone peripheral to the cement called the neocortex, and/or a radiolucent zone of fibrous tissue between the cement and this bone (Charnley[a], 1970; Willhert *et al.* 1974). Loosening is also associated with stem migration or subsidence. Early migration, as detected by roentogen stereophotogrammetric analysis (RSA) can predict early loosening (Karrholm *et al.* 1994; Ryd *et al.* 1995). For migration of the implant to take place the bone-prosthesis interface must have a soft tissue membrane. This membrane may be maintained by movement (Aspenberg *et al.* 1992). Fracture of acrylic bone cement (Weber and Charnley, 1975; Amstutz *et al.* 1976; Carlsson *et al.* 1977; Beckenbaugh and Ilstrup, 1978;) and radiolucent lines at the stem-cement interface (Charnley, 1975; Fornasier and Cameron,

1976; DeSmet *et al.* 1977;) are also characteristics associated with early prosthetic loosening.

In 1983 a study that examined 258 Stanmore massive prostheses (Scales and Wright, 1983) demonstrated that the common complicating factors associated with these implants were infection (5.4%), implant fracture (2.7%) and aseptic loosening (1.9%). More recently, another study (Ward *et al.* 1991) demonstrated that aseptic loosening was the major cause of bone tumour implant failure. Unwin *et al.* 1995 showed that the probability of a patient surviving aseptic loosening for 120 months was 93.8% for a proximal femoral replacement, 67.4% for a distal femoral replacement and 58% for a proximal tibial implant. It was found that young patients with distal femoral prostheses where a high percentage of the proximal femur was replaced had the poorest prognosis for survival. The percentage of bone removed had a significant effect on survival in the proximal tibial replacement group, but the age of the patient did not. By contrast, neither the age nor the amount of bone resected affected the survival of proximal femoral implants.

The 1976 classification of the mechanical modes of failure of cemented stem-type femoral components was designed to help understand the process of stem loosening (Amstutz *et al.* 1976; Gruen *et al.* 1979). This classification identified four modes of failure:

Mode I: pistoning of the metal stem within the cement mantle; or of the cement mantle within the femoral canal.

Mode II: medial mid-stem pistoning characterised by proximal medial migration and distal lateral migration.

Mode III: transection site pivot, where there is toggling of the distal end of the stem.

Mode IV: cantilever fatigue where there is continual medial migration while the distal stem remains rigidly fixed.

Figure 1: Aseptic loosening of a distal femoral bone tumour replacement: 21 months after surgery.

The exact mechanism for loosening is complex and not fully understood. A number of interdependent factors affecting loosening are thought to exist. In the 1960's and 1970's certain design features, such as small stems (Beckenbaugh and Ilstrup. 1978), and stems with sharp corners, contributed to the high rate of loosening in patients. Poor cementing techniques were

also a contributing factor. Since then, these factors have been addressed and it is now accepted that there are two factors that appear important in the aetiology of prosthetic loosening. The first is a lack of initial implant stability (Freeman and Plante-Bordeneuve, 1994; Walker *et al.* 1995). The second factor is the presence of particulate wear debris.

1.2.1 LACK OF INITIAL STABILITY ASSOCIATED WITH PROSTHETIC LOOSENING

A less than optimal surgical technique is the primary cause of initial stem instability (Martens *et al.* 1974; Muller, 1974; Amstutz *et al.* 1991;). Other factors include the quality of bone stock present at the time of surgery, patients weight, and activity of the patient after surgery. In addition weight and loading are especially important factors for femoral component durability because of cantilever bending (Chandler *et al.* 1981; Schurman *et al.* 1989; Amstutz *et al.* 1991;) as well as varus-valgus orientation of the prosthesis (Galante *et al.* 1975; Andriacchi *et al.* 1976; Markoff and Amstutz, 1976; Beckenbaugh and Ilstrup, 1978). An increased offset simultaneously increases the bending moment on the prosthesis, and may increase the strain in the medial cement mantle (Johnson *et al.* 1979). The correct stem length is important. Mixing and insertion influence the strength (UTS) of the cement. This effects the quality of the cement-stem interlock and interdigitation of the cement with cancellous bone. It has become increasingly apparent over recent years, that debonding of the cement-metal interface is a common occurrence and may be a critical precursor to implant failure (Jasty *et al.* 1992). The surfaces of some stem designs are grit-blasted and in some instances porous-coated to increase the tensile bonding strength of the cement-prosthesis interface (Davies and Harris, 1994, Cameron, 1994). Crowninshield and Tolbert, 1983 have shown that compared with a bonded interface, the strains in the cement mantle increase by a factor of two when there is no bond between the cement and metal surface of the prosthesis. Several finite element analysis studies have confirmed this (Huiskes 1979;

Hampton *et al.* 1981; Harrigan and Harris, 1991) and these studies concluded that failure of the cement-metal interface was a major cause of implant loosening. However, a strain gauge study performed by Miles (1990), demonstrated that the shear stress at the cement-bone interface is higher when the cement is bonded to the stem than when the stem is smooth. Miles also pointed out that a smooth stem produced higher radial compressive loads, which encouraged the cement to creep into the adjacent bone, resulting in a system better able to adapt to bone remodelling at this interface. Lee, 1990 confirmed these findings in a separate study. A study by Schmalzried, 1998 investigated stem-cement debonding in a smooth metal hip stem, a grit blasted stem and a stem that had been pre-coated with PMMA prior to implantation. This study found that stem-cement debonding occurred in all three cases. At the interface of the grit blasted stems they found that once debonding had occurred, relative motion between this surface and the cement generated cement and metal particles. They reported that these particles caused stem burnishing, third body damage at the articulation and osteolysis with characteristic plump macrophages containing cement and metal debris. They concluded that debonding from a smooth metal stem is not necessarily detrimental, and may in part be necessary for clinical success. They based their conclusion on follow-up studies which reported on well functioning Charnley hips where 38% of the cases showed radiolucent lines in zone 1 at the stem-cement interface. None of these cases reported clinical loosening, or showed visible cracks in the cement mantle or osteolysis. Schmalzried (1998) also reported FEA results where they found that stems with low interfacial bond strength could de-bond without compromising the integrity of the cement mantle. With higher bond strength, crack propagation was more likely to proceed into weaker regions resulting in failure of the cement mantle.

In order to achieve initial stability, optimal preparation of the bone surfaces by cleaning and drying the bone surface to minimise the mixture of blood with acrylic cement is also required. The appropriate timing for the insertion of the cement until polymerisation has been shown to be important (Watson and

Stulberg, 1989). Inadequate filling of the medullary canal with polymethylmethacrylate is considered to be a factor that contributes to loosening (Beckenbaugh and Ilstrup, 1978; Carlsson and Gentz, 1980). Harris, 1975 recommended injecting the cement with a cement gun, and Amstutz *et al.* 1976 proposed plugging the femoral canal prior to injection to improve cement pressurisation. Oh *et al.* 1978 showed that compared with non-plugged femora, plugging the medullary canal in a cadaver study increased the pressure in the cement upon insertion of the stem. They also demonstrated that using a distal plug improved distribution of the cement throughout the medullary canal into the interstices of the cancellous bone with increased strength of the cement-bone interface and fewer voids, defects, and laminations in the cement.

In 1975, the importance of reducing the porosity of the cement in order to improve its mechanical properties was first recognised and studied (Bayne *et al.* 1975). The fatigue failure of bone cement is a recognised mode of failure. There is strong evidence that cracks in the cement are initiated at voids which act as stress risers (Carter *et al.* 1982; Gates *et al.* 1983; Burke *et al.* 1984) particularly at the stem-cement interface. The preferential formation of voids at this site results from shrinkage during polymerisation and shrinkage of the cement towards the warmer cement-bone interface (Bishop *et al.* 1996). A study tried to resolve this problem by pre-heating the stem at 44^0C before insertion in order to reduce porosity at the stem-cement interface (Bishop *et al.* 1996). This study reported that preheating the stem dramatically reduced porosity at the stem cement interface and concluded that this concept could significantly increase the life of hip arthroplasties. Other mechanisms which generate voids in the cement include air entrapment during mixing under atmospheric conditions (Debrunner *et al.* 1976; Fumich and Gibbons, 1979; Eyerer and Jin, 1986; Linden, 1988), presence of air spaces between the polymer beads, void generation owing to evaporation or boiling of monomer (Debrunner *et al.* 1976), thermal expansion of existing voids and the presence

of cavitation voids (Chan and Ahmed, 1991). It has been known for some time that centrifugation of the cement leads to a reduction in porosity and greatly prolongs fatigue life (Burke *et al.* 1984; Gates *et al.* 1984; Davies *et al.* 1987; Davies[a] *et al.* 1987). Mixing under partial vacuum reduces porosity and has been extensively explored (Lidgren *et al.* 1984; Arroyo, 1986; Lidgren *et al.* 1987; Wixon *et al.* 1987). Ultrasonic agitation has also been investigated (Saha and Warman, 1984), but requires further study. Innovations in new bone cements and new application techniques are also being examined (Jansson, 1994; Larsen *et al.* 1995) with the purpose of reducing the adverse effects involved in cementation. These adverse effects include initial bone necrosis due to exothermic cement polymerisation temperatures (Linder, 1976; Noble; 1983) and impairment of the local blood circulation (Lindwer and Hooff, 1975; Linder, 1977; Sturup *et al.* 1990). These two factors have been shown to encourage membrane formation at the cement-bone interface (Goldring *et al.* 1983; Linder and Carlsson, 1986; Malefijit *et al.* 1987; Jensen *et al.* 1991). Thus a new cement under development by Larsen *et al.* 1995 is characterised by having a lower exotherm on setting, a low release of monomer, a low residual content of monomer with the retained physical properties of methylmethacrylate cement. A separate study has introduced hydroxyapatite composite resin as a new type of bioactive bone cement. This bioactive cement had superior mechanical properties to PMMA and also has the property of achieving direct contact with bone (Saito *et al.* 1994).

1.2.2 WEAR DEBRIS AND ITS ROLE IN PROSTHETIC LOOSENING

Two of the early concerns regarding the use of bearing surfaces in joint arthroplasty were the limited life expectancy of the prosthesis as a result of wear and the loosening torque that results from friction (Friedman *et al.* 1993). It is now apparent that the principle problem is the quantity of wear debris that is produced from bearing surfaces. It has been well documented that wear debris stimulates cellular osteolysis (Harris *et al.* 1976; Willhert *et al.* 1977; Willhert and Semlitsch, 1977; Skinner and Mabey, 1987; Howie *et al.* 1988).

Further studies have demonstrated that wear particles also result from corrosion mechanisms seen with taper joints, porous coatings, and screws (Black, 1993; Maloney and Jasty, 1993). Wear debris is produced primarily through three mechanisms: abrasion, adhesion and fatigue. Wear debris can also produce three-body abrasion accelerating the wear at the articular surfaces. Many studies have reported on new methods to minimise the amount of wear debris produced, for example, by using optimal material combinations at the articulating surfaces. The surface hardness of certain materials can be increased by various treatments such as ion implantation and nitriding (mainly used in total knee replacements). The design of total knee components is continually being modified in an attempt to reduce contact stresses and thus wear (Crowninshield *et al.* 1991; Alexander *et al.* 1991). A recent modification increased the conformity of the bearing in order to reduce focal points of high contact stresses that result in sub surface cracking and delamination of the polyethylene. However, the wear of a bearing surface is an inevitable consequence of the activity of the joint and so the more active the patient is, the greater the amount of wear debris released. Therefore the younger and more active patients are more prone to aseptic loosening (Charnley *et al.* 1969; Hierton *et al.* 1983; McCoy *et al.* 1988; Wroblewski, 1988;).

An initial radiolucent line of osteolysis, which later expands into the cortex, has been described in association with implants fixed using methylmethacrylate bone cement (Johnson and Crowninshield, 1983; Jones and Hungerford, 1987; Lombardi *et al.* 1989; Maloney *et al.* 1990; Maloney[a] *et al.* 1990; Santavita *et al.* 1990). In the case of acetabular components, loosening starts at the rim and progresses towards the dome of the cup. At first osteolysis was thought to result from fragmentation of the cement mantle and was termed "cement disease" (Jones and Hungerford, 1987). It has now been shown that osteolysis results from a foreign body reaction to particulate PMMA, metal and polyethylene wear debris (Goldring *et al.* 1983; Linder *et al.* 1983; Johanson *et al.* 1987; Howie *et al.* 1988; Lombardi *et al.* 1989;

Maloney[a] *et al.* 1990; Schmalzried *et al.* 1992; Willhert *et al.* 1990; Cooper *et al.* 1992; Kim *et al.* 1993;). Although these particles have been shown to activate macrophages *in vitro (*Glant *et al.* 1992; Shanbag *et al.* 1993), the predominant particle that causes osteolysis *in vivo* appears to be ultra-high molecular weight polyethylene (Howie *et al.* 1988; Amstutz *et al.* 1992; Friedman *et al.* 1993;). A recent study by Rakshit *et al.* 1998 investigated the relationship between wear particles and macrophages. They concluded that different wear particles stimulated different receptors on the surface of the macrophage. The extent of the macrophage reaction and hence the extent of bone loss, depended on which receptors were stimulated.

In recent years, the importance of the synovial membrane-like structure which develops at the bone-cement interface has been studied. The initial development of this membrane appeared to result from a biological response to the introduction of polymethylmethacrylate. This response occurred due to the mechanical, chemical and thermal-induced trauma to bone when the cement was inserted (Willhert and Semlitsch, 1976; Willhert and Semlitsch, 1977). Repair was associated with the formation of granulation tissue and osteoclastic resorption of necrotic bone, culminating in the development of a thin fibrous membrane between cement and viable bone (Eftekher *et al.* 1985). However, separate studies by Malcolm, 1991 and Linder and Hansson, 1983 have identified viable bone in direct contact with the cement interface. Studies of the fibrous tissue interface surrounding well-fixed and functioning implants have demonstrated a predominantly collagenous tissue, lacking inflammatory cells with occasional macrophages and few cement particles (Charnley, 1970; Freeman *et al.* 1982; Goodman *et al.* 1985). In contrast, the peri-prosthetic membrane retrieved after prosthetic failure due to aseptic loosening is thickened and contains a pronounced histiocyte and giant cell infiltration with fibrosis and necrosis (Goldring *et al.* 1983; Eftekher *et al.* 1985; Bullough *et al.* 1988). Particles of cement, polyethylene and metal are present throughout the membrane at both intracellular and extracellular sites (Herman *et al.* 1989). The severity of the response appears to correlate with

the duration of implantation (Johanson *et al.* 1987). The amount of wear debris correlates with cellular response, lysis of bone, and loosening (Semlitsch *et al.* 1977; Rae, 1981). This characteristic change in the appearance of the interface has led many investigators to propose that macrophage phagocytosis of cement, metal and UHMWPE particles leads to the production of mediators which stimulate bone resorption at the interface (Freeman *et al.* 1982; Radin *et al.* 1982; Goldring *et al.* 1983; Bell *et al.* 1985; Lennox *et al.* 1987; Galante *et al.* 1991; Horowitz *et al.* 1993).

The presence of wear particles at locations distant from the articulation often within local osteolytic cavities in cortical bone led to the concept termed the effective joint space, described by Schmalzried[a], 1992. Due to debonding of the cement from the alloy stem the synovial cavity is in continuity with the cement-stem interface. It was suggested that a path exists around this peri-prosthetic region for the passage of debris. This is thought to occur through a fibrous tissue layer (Schmalzried, 1992; Schmalzried[a] *et al.* 1992). Cracking and fracture through the cement mantle allows the passage of wear debris to the cement-bone interface. Prosthetic loading and movement of the synovial capsule results in a pumping mechanism in which wear debris laden synovial fluid is forced along the interface throughout the effective joint space, depositing wear debris at sites distant from the articulation (Anthony *et al.* 1990).

Fibroblasts have also been reported to show proliferative responses *in vitro* after exposure to metal particles (Maloney[a] *et al.* 1993). Particulate debris and cell death are well known activators of macrophages and can trigger further macrophage cell recruitment, phagocytosis, and the release of osteolytic factors. Prostaglandin E_2 (PGE_2) is an inflammatory mediator associated with bone resorption (Klein and Raisz, 1970; Minkin and Shipiro, 1986 Tashjian *et al.* 1987; Collins and Chambers, 1992; Collins and Chambers[a], 1992). PGE_2 is also produced in association with aseptic

loosening (Horowitz *et al.* 1994). Evidence to support a role for this mediator in loosening has been obtained in an *in vivo* study. This study showed how the PGE_2 levels in the synovial fluid from loose prostheses were significantly higher than that found in well-fixed cemented prostheses (Horowitz[a] *et al.* 1991). Macrophages are capable of producing PGE_2 in response to inflammatory stimuli (Kurland and Bockman, 1978; Bockman, 1981), and so the mechanism of aseptic loosening may involve PGE_2 production by macrophages at the interface in response to particle phagocytosis. However, there are other cell types at the interface, such as osteoblasts, which are also capable of producing PGE_2 (Sudo *et al.* 1983; Tashjian *et al.* 1987). In addition, these cells produce PGE_2 in response to mediators released from macrophages exposed to inflammatory stimuli (Tashjian *et al.* 1987; Rapuano *et al.* 1991). Therefore, clarification of the direct or indirect role of the macrophage in loosening still needs to be determined. Horowitz *et al.* 1994 proposed that the role of the macrophage at the interface is primarily to phagocytose cement particles and to release small amounts of mediators (not PGE_2) which in turn stimulate the osteoblast to produce larger amounts of mediators, such as PGE_2. These mediators propagate the inflammatory response and ultimately lead to bone resorption possibly through a PGE_2-osteoclast-mediated mechanism (Vaes, 1988; Pollice *et al.* 1993).

Macrophages are also known to secrete the inflammatory mediator tumour necrosis factor ($TNF\alpha$) (Horowitz *et al.* 1993), a cytokine also known as osteoclast-activating factor (Campbell *et al.* 1991). Macrophages are known to induce bone loss by releasing such mediators as the tumour necrosis factor α which stimulates PGE_2 release from osteoblasts (Tashjian *et al.* 1987) as well as directly by the release of oxide radicals and hydrogen peroxide (Horton *et al.* 1972; Mundy *et al.* 1977; MacArthur *et al.* 1980; Dominguez and Mundy, 1988). A study has proposed that macrophages themselves are capable of resorbing bone (Campell *et al.* 1990). *In vitro* studies have shown the ability of particle activated macrophages to resorb bone by the production

of proteolytic enzymes (Herman *et al.* 1989; Athanason *et al.* 1992). Another study has shown how macrophages with phagocytosed particulates are capable of differentiating into cells that have all the properties of an osteoclast (Sabokar *et al.* 1997).

Another potent osteolytic factor produced at the loose implant interface is interleukin 1(IL 1) (Goldring *et al.* 1983; Stashenko *et al.* 1987; Coe *et al.* 1989; Kim *et al.* 1990). IL 1 is synthesized by several cell types including fibroblasts, endothelial cells and macrophages (Campell *et al.* 1991) and while it may have the potential to simulate the osteoclast, it is thought that this role is largely mediated by tumour necrosis factor α (Gowen *et al.* 1983). Both TNFα and IL 1 provide activation signals to lymphocytes (Brennan and Feldmann, 1992) that in turn are thought to release further cytokines namely IL 2, IL 6 and Interferon (IFNγ), which influence osteoclastic activity and bone remodelling (Bando *et al.* 1993).

An interesting study performed by Aspenberg and Herbertsson,1996 questioned the effects of movement on the peri-prosthetic fibrous tissue membrane and compared it with the effects of particulate debris. They did not find osteolysis at a stable interface, unless accompanied by infection. On the application of movement, they found that localised areas of bone resorption and soft-tissue metaplasia occurred and the later introduction of particles appeared only to have minor effects. The only situation when an effect from the particles was seen was when a fibrous tissue layer had been created and then left without further movement. In the presence of the particles the membrane was preserved whereas without particles it changed back into bone. They concluded that the presence of particles was an effect of prosthetic loosening rather than a cause and suggested that mechanical stimuli are of primary importance for prosthetic loosening, and that particles may modulate the later stages of the loosening process. However, in their model they used particles of a larger size than those occurring around loose

implants in the human, and also there was no joint cavity and so no definite conclusions can be drawn from this study. However, it highlights the increasingly reported speculation of a possible synergistic coupling between mechanical and biologic events which precipitates aseptic loosening. Aspenberg took this study father by looking at the effect of fluid pressure at the implant interface (Aspenberg and Van der Vis, 1998). They allowed an implant to osseointegrate on a rabbit tibia and then applied pressurised fluid and movement to the implant interface. They found that osteolysis was seen in all cases.

While aseptic loosening of joint replacements is often a result of wear particle induced osteolysis, the loosening of cemented intramedullary stems used to fix massive segmental bone tumour prostheses is often more mechanical in nature. During surgery, and in order to remove and clear the area surrounding a bone tumour and to insert the prosthesis, many muscles and tissue are resected. During the normal walking cycle, these muscles are important in movement as they apply a combination of compressive and bending loads to the femur. An incomplete set of muscles, especially when the greater trochanter has been resected (a site where a large number of abductor muscles insert), results in the application of significant bending moments to the implant and bone especially at the transection site between the two. At this site and largely due to the differences in the elastic moduli between titanium, PMMA and bone, micromovement occurs during dynamic loading. This micromovement results in the deterioration of the prosthesis-cement and cement-bone interfaces thus resulting in aseptic loosening of the intramedullary stem. Another commonly observed feature is resorption of unloaded bone at the shoulder of the implant. It is thought that this gap may be an important initiator where undue stress may transfer to the cement mantle resulting in failure of the cement. Radiolucent lines at both the cement-bone and cement-implant interfaces are often observed suggesting that this loosening process may be increased by the ingress of wear debris following soft tissue wear of the titanium implant shaft.

1.3 UNCEMENTED FIXATION

The use of modern cementing techniques has resulted in a significant reduction in the incidence of aseptic loosening of cemented femoral components in primary arthroplasties. Using contemporary techniques, Harris and McGann, 1986 and Russotti *et al.* 1988 reported the incidence of aseptic loosening of the femoral component to be 1.7% and 1.2% respectively at a minimum 5 year follow-up period. Mulroy and Harris, 1990 reported a 3% failure rate with cement at 11 years. However, at 3 year follow-up D'Antonio and co-workers (D'Antonio *et al.* 1992 and D'Antonio[a] et al. 1992) reported a 0.46% incidence of aseptic loosening of HA coated femoral stems. At 2 year follow-up Geesink, 1990 and Tonino *et al.* 1995 found no cases of aseptic loosening in their series. Another study by D'Antonio, 1996 reported a failure rate of 0.7% in HA coated femoral stems at 5 year follow-up. Vedantam and Ruddlesdin, 1996 reported a 1.85% failure rate for HA coated femoral stems and 3.7% for HA coated acetabular components at 2 year follow-up. Engh, 1995 reported from their study an overall failure rate of 0.6% at 11 years with non-HA coated cementless femoral components. Radiographic analysis of HA coated stems demonstrated a low incidence of radiolucencies at the interface, the presence of spotwelds (which have been characterised as evidence of bone growth to the implant surface), a high incidence of cancellous condensation at the transition from coated to uncoated stem and periosteal cortical hypertrophy at the mid and distal stem. All of these characteristics represent adaptive bone remodelling around well fixed uncemented implants. Therefore, within the time frame of existing data, cementless fixation of some designs compares favourably with cemented fixation.

Methylmethacrylate provides a poor surface for cell adhesion (Ratner *et al.* 1975) which suggests that the physio-chemical characteristics of this material may prevent ingrowth or cellular attachment. In contrast, studies involved with cementless fixation demonstrated that direct bone-implant contact was achieved and could maintain sufficient stability of the prosthesis (Pilliar *et al.*

1975; Spector *et al.* 1978; Bobyn *et al.* 1982; Hedley *et al.* 1982; Chen *et al.* 1983). In 1977, a study by Branemark used the term osseointegration to describe this fixation where the implants were anchored by the direct attachment of bone. Osseointegration is defined as "a direct, on the light microscopical level, contact between living bone and implant" (Albrektsson, 1981).

Osseointegration is influenced by both the biomechanical forces and biomaterial properties of the implant (Freidman *et al.* 1993). The forces transmitted between the implant and bone depend on the design of implant, the materials used, and the mechanical characteristics of the surrounding bone. The biomaterial properties of the surface affect the degree of fixation.

The materials currently used in cementless implant fixation are commercially pure titanium, titanium alloy (used for porous coatings), cobalt chrome (used for sintered and plasma sprayed coatings) and hydroxyapatite.

1.3.1 POROUS COATINGS

Porous-coated uncemented implants were designed for stabilisation by ingrowth of bone into interconnecting porosities (Hedley *et al.* 1982; Haddad *et al.* 1987). This has been achieved in porous hip implants inserted into experimental animals (Harris *et al.* 1983; Spector *et al.* 1983) and to a lesser degree, in components retrieved from humans (Cook *et al.* 1988; Jasty *et al.* 1988). Most studies that have examined retrieved components removed for reasons other than loosening have found some degree of bone ingrowth into the pores (Brooker and Collier, 1984; Bobyn and Engh, 1984; Engh *et al.* 1987; Cook *et al.* 1988; Cook *et al.* 1988(b)). The mean extent of ingrowth has been reported to be in the range of 5% (Cook *et al.* 1988; Cook *et al.* 1988(b)) to 40% (Jacobs *et al.* 1989) of the available pore volume. It has been established that bone formation will occur within a porous surface when the implant is well-fixed and minimal movement occurs between the implant and

bone surface (Cameron *et al.* 1973). Movement prevents the calcification of tissue within the pores and results in fibrous tissue attachment only. A tight press fit is required for initial stability and an advantage of this is that the porous implant lies close to the bone. This results in a more rapid rate of bone ingrowth into the pores (Cameron, 1976). Harris *et al.* 1983 inserted porous coated acetabular cups into dogs. They reported that in one case bony ingrowth was sparse and unable to bridge a 0.5mm gap at the interface. In contrast, cups that lay in close proximity to the implant demonstrated bone ingrowth that penetrated at least three layers of sintered beads.

Several studies have investigated bone ingrowth into porous systems of different pore size. Effectively, bone will grow into pore sizes from 25μm up to a few millimetres in diameter (Cameron 1994). The fastest rate of ingrowth was seen in sizes ranging from 50 to 400μm (Bobyn *et al.* 1980; Bobyn *et al.* 1982). Most pore sizes are manufactured in the range of 100 to 350μm (Cameron, 1994). The average pore volume is 30%. The shape of the pore (whether symmetrical or irregular) does not influence the amount of bone ingrowth (Cameron, 1994). Chao and Sim, 1985 and Malawar *et al.* 1989 investigated the response of bone to porous coatings following application onto the surface of massive segmental replacements in an animal model. These studies concluded that the porous coating encouraged bone to bridge over the shaft of the implant joining the two segments of bone. The authors postulated that such bridging might improve the transfer of stresses and diminish implant loosening.

A porous coating is usually applied to an implant surface by one of three methods – sintering, diffusion bonding or plasma spray processing (Bourne *et al.* 1994). The sintering technique produces a porous coating composed of layers of spherical beads. The sintering process is a heating process that fuses the beads to the substrate and each other. The bond strength of the porous layer is controlled by the duration and temperature of the heating

cycle. Porosity is controlled through bead size. Diffusion bonding results in titanium fibre metal pads attached to titanium alloy substrate using heat and pressure. The titanium fibre metal pads are positioned into recesses in the substrate and porosity is controlled by the configuration of the wire and by temperature and pressure. The plasma spray technique sprays molten titanium onto the substrate surface. The characterisation of this porous coating are controlled through variations in particle size and pressure. Many studies still debate which of these coatings is optimal in terms of encouraging maximal amounts of bone ingrowth (Klawitter *et al.* 1976; Turner *et al.* 1986; Collier *et al.* 1988; Cook[a] *et al.* 1988).

Porous-coated surfaces have been applied to hip and knee prostheses to encourage osseointegration. Several reports investigating the short-term clinical outcome of porous-coated uncemented implants have demonstrated good results (Engh, 1983; Engh *et al.* 1987; Hedley *et al.* 1987; Callaghan *et al.* 1988). However, consensus is that the early results of uncemented implant arthroplasty may not be as good as the conventional contemporary cemented implants (Haddad *et al.* 1987; Spector, 1987). A 10% incidence of intraoperative femoral fractures has been reported and attributed to the difficulty in accurately press-fitting the uncemented component to the bone (Jasty, 1994). Early subsidence rates of 4 - 10% thought to be due to inadequate initial rotational stability have also been reported (Hungerford, 1993; Kim and Kim[a], 1993). A further clinical problem associated with uncemented hip implants with incidences up to 30% is thigh pain where revision is required despite solid fixation of the implant (James, 1989). Cameron *et al.* 1990 reported that the modulus mismatch between the implant and the femur may be a contributing factor to end-of-stem pain. Of concern at 5 to 6 year follow-up is the increasing incidence of peri-prosthetic osteolysis (Tanzier *et al.* 1992). In order for the uncemented implant to fit the medullary cavity these components are manufactured comparatively larger than their cemented counterpart. Their increased size increases their

stiffness, which is proportional to the fourth power of the radius. The surrounding bone is stress protected and undergoes subperiosteal resorption. Many studies have reported how bone resorption increases in severity with the larger and stiffer stems (Engh and Bobyn, 1988; James, 1989; Natarajan *et al.* 1990; Bobyn *et al.* 1992). Studies have concluded that more flexible, or isoelastic implants are required to reduce stress shielding and thigh pain (Spector, 1988; Cameron *et al.* 1990; Bobyn *et al.* 1990; Jalim *et al.* 1988). Thinning and loss of the cortex around uncemented porous implants, especially those that are fully or nearly fully coated, have been reported in many animal studies and in some early human clinical studies (Lord and Bancel, 1983; Turner *et al.* 1986; Engh and Bobyn, 1988). Initially, a complete circumferential porous coating was applied to the implant surface. This was based on the assumption that osseointegration would form a seal around the implant. However, more recent studies have reported bone loss to be most severe when the entire surface of the femoral component was porous coated (Bobyn *et al.* 1987; Engh and Bobyn, 1988). These concerns have limited the use of the porous surface to the proximal region on a femoral stem (Bobyn *et al.* 1987; Callaghan *et al.* 1988; Jasty *et al.* 1989). However, the AML implant still retains a coating over the entire surface of the stem and although extensive stress shielding and bone resorption occurs, this implant shows a survivorship almost equal to that of cemented implants.

Other studies conclude that the long-term stability of the implant is not dependent on bone growth into the porous structure, but on the initial fit of the stem in the diaphysis (Albrektsson *et al.* 1981; Zweymuller, 1986). Some authors have concluded that porous coatings on implant surfaces may not be necessary since bone can osseointegrate with smooth and rough metal surfaces (Albrektsson *et al.* 1981). They conclude that the long-term stability of prostheses is only dependent on the fit and fill of the components within the canal. Nevertheless, many studies continue to investigate ways of improving bone ingrowth into a porous coating.

Porous metal has a limited osseoconductive capacity. Therefore many surgeons when inserting an uncemented porous component use it in conjunction with auto or allo bone grafts. Soballe, 1992 has shown how the presence of a bone graft significantly enhanced bone bonding to the implant. Other studies have investigated ways to enhance bone ingrowth to the porous surface. A hydroxyapatite coating has been applied to the porous surface (Jarcho *et al.* 1971; Spector, 1987; Ducheyne and Healy 1988; Cook *et al.* 1991; Cook[a] *et al.* 1991; Moroni *et al.* 1992; Kay 1987; McPherson *et al.* 1995). Some studies have reported there to be no clinical advantage in the use of hydroxyapatite (Spector, 1987; McPherson *et al.* 1995). Other studies have reported a significant increase in bone ingrowth (Ducheyne and Healy 1988; Moroni *et al.* 1992). Cook *et al.* 1991; Cook[a] *et al.* 1991; Cook *et al.* 1992 reported that hydroxyapatite coated porous surfaces encouraged bone ingrowth even when a millimetre gap existed between the implant and host bone. Studies investigating hydroxyapatite coatings on porous surfaces have demonstrated an early increase in the strength of attachment at six weeks (Berry *et al.* 1986; Rivero *et al.* 1988).

1.3.2 HYDROXYAPATITE

Synthetic hydroxyapatite (HA) is a safe, non-toxic, highly biocompatible material (Manley, 1993). Many animal studies as well as human retrievals have demonstrated how HA is able to conduct bone formation along its surface. Clinical results of HA coated implants at 6 to 8 years are excellent (D'Antonio *et al.* 1992; Geesink, 1993). Blocks of HA (Jarcho, 1981; Holmes and Haglar, 1987; Krajewski. 1988; Oonishi, 1991) and coatings of HA on metal substrates (Ducheyne *et al.* 1980; de Groot *et al.* 1987; Geesink *et al.* 1987; Cook and Thomas 1988; Geesink *et al.* 1988) have shown early bone apposition and excellent biocompatibility. Bone apposition appears to be well advanced as early as 3 weeks, (Bloebaum, 1991; Hayshi, 1991) and in some studies, HA has shown greater than 90% bone apposition at 96 weeks

(Hayshi, 1991)· Most authors have shown no evidence of fibrous membranes and have shown attachment strengths equivalent to or stronger than porous coatings (de Groot, 1987; Cook, 1992).

In 1932, Klement as cited by Engstrom identified the chief constituent of bone mineral as the calcium phosphate ceramic hydroxyapatite ($Ca_{10}(PO_4)_6(OH_2)$). Since then, and after 65 years of research and improved manufacturing techniques, synthetic hydroxyapatite and calcium phosphate coatings have a similar chemical and crystallographic structure to bone (Engstrom *et al.* 1972; Jarcho, 1981; Klein *et al.* 1983; de Groot, 1983; Jarcho, 1986; Ducheyne and Lemons, 1988; Koeneman *et al.* 1990). For this reason, synthetic hydroxyapatite is compatible (osteogenic cells will readily attach to and proliferate on its surface (Bauer *et al.* 1991; Kirschenbuam, 1991) and is capable of forming a direct biochemical bond with bone. Hydroxyapatite exists over a compositional range characterised by its calcium to phosphate ratio. It can vary from stoichiometric hydroxyapatite with a calcium to phosphate ratio of 1.67 to calcium deficient hydroxyapatite (α and β tricalcium phosphate) with a calcium-to-phosphate ratio of 1.5. The method of manufacture of calcium-phosphate compounds and the temperature to which they are exposed determines the ceramic properties. Commercially available calcium-phosphate materials include biphasic calcium phosphate (mixed β-tricalcium phosphate and hydroxyapatite phases), β-tricalcium phosphate, hydroxyapatite, non-sintered calcium-phosphate powders, coralline hydroxyapatite, and bone derived materials (Legeros, 1993). The exact physiologic process of bonding has not yet been elucidated, but it has been hypothesised that the ceramic liberates calcium and phosphorous ions that stimulate bone-healing activity in the surrounding bone (Soballe *et al.* 1993). The ceramic coating is also thought to adsorb bioactive factors that initiate bone formation directly onto the ceramic surface. Under light microscopy, mesenchymal cells at different stages of differentiation can be seen both on the surface of retained bony trabeculae and on the hydroxyapatite coating

(Hardy *et al.* 1991). Many of these poorly differentiated cells seem to develop into osteoblasts that later synthesise an osteoid material. This leads to bidirectional bone formation (Soballe *et al.* 1993), with osteogenesis from the implant surface towards the surrounding bone and from the surrounding bone towards the implant surface. Walker and Katz, 1983 studied bonding of bone to various calcium containing minerals. They concluded that carbonate groups in bone collagen attached to the mineral surface and bonded the bone to the implant. However, they did not examine the role of the inorganic mineral fraction of bone in bonding. Several investigators have shown the increased mechanical strength of the bone-implant interface when a hydroxyapatite coating is applied to metal alloy surfaces (Geesink *et al.* 1987; Thomas *et al.* 1987; Cook and Thomas, 1988; Geesink *et al.* 1988; Rivero *et al.* 1988; Geesink, 1990; Bauer *et al.* 1991; Dherit *et al.* 1991; Dherit[a] *et al.* 1991; Hayashi *et al.* 1993; Hayashi[a] *et al.* 1993). Both transmitted light microscopy (Ducheyne *et al.* 1980; van Blitterswijk *et al.* 1986; Thomas *et al.* 1987; Cook *et al.* 1988) and scanning electron microscopy (Denissen *et al.* 1980) have shown that the newly formed bone on hydroxyapatite is identical to normal cortical bone. This bone which is in direct contact with the implant was reported in both animal studies and human post-mortem material to have elevated levels of calcium (Cook *et al.* 1988; Geesink *et al.* 1988). This highlights the hypothesis that free calcium and phosphate at the surface of HA allows a bioactive reaction with the surrounding bone (Geesink *et al.* 1988). It has been suggested that the hydroxyapatite must first partially dissolve, thereby increasing the concentration of calcium and phosphate in the microenvironment. Carbonate apatite microcrystals then form and associate with the organic matrix of bone, causing biological growth of bone tissue (Legeros and Orly, 1991).

However, the brittleness and poor tensile strength of HA limits its effectiveness in many load-bearing situations (de Groot *et al.* 1981). Hence HA is usually coated onto a metal substrate. A HA coating of 100-150μm may

suffer fatigue under tensile loading. During the first few months post implantation, approximately 10 -15μm of HA will dissolve away from the coating (Geesink *et al.* 1988). These factors questioned the optimal thickness of HA. Presently, a coating of 50μm is considered optimal. A further advantage following the application of a HA coating is that it is thought to prevent the release of metal ions from the underlying alloy (Ducheyne and Healy, 1988).

Although there are many techniques for the application of a hydroxyapatite coating to a metal surface (Compaction (Zimmerman *et al.* 1990), electrophoresis, dipping and sputtering (vacuum deposition (Ducheyne *et al.* 1986; Kay, 1988)), the most extensively used has been the plasma spray technique (Koeneman *et al.* 1990). The ceramic powder is introduced into a flame that directs particles for deposition onto the metal surface. It has recently been demonstrated that the quality of plasma-sprayed deposited coatings can be influenced by several parameters. These include the temperature of the plasma, the nature of the plasma gas, the particle size of the powder, and the chemical nature of the ceramic powder (Wolke *et al.* 1992). More recent techniques such as low-pressure plasma-spraying are being developed to provide a coating that is both stronger and more resistant to dissolution (Edwards *et al.* 1991). *In vitro* dissolution experiments showed how changes in the particle size distribution influence the dissolution rate of a HA coating (Klein, 1991). However, the *in vivo* effect of this is not known. Therefore, all HA coatings are not identical in their composition, crystallinity, density, purity and structure. This affects the coatings bioactivity and bioresorbability. Advantages for the use of the plasma spray process include simplicity, high deposition rates and low substrate temperature (Cheang and Khor, 1996). However, several studies have reported concern over the consistency and reliability of the HA coating quality following this technique (Koch *et al.* 1990; Whitehead *et al.* 1993; Khor and Cheang, 1994; Wang *et al.* 1995;). These studies demonstrated variables associated with the process which influence the microstructure and properties of the final hydroxyapatite

coating. Studies suggested that the HA starting powder can change its crystallinity and phase compositions after experiencing plasma spray deposition (Koch *et al.* 1990; Whitehead *et al.* 1993; Wang *et al.* 1995). This is demonstrated by HA coatings that are often more soluble both *in vivo* and *in vitro.* This decrease in solubility is thought to be due to a decrease in crystallinity (Thomas and Cook, 1992) and an increase in induced calcium phosphate phases (Koch *et al.* 1990; Ducheyne *et al.* 1993) not present in the starting powders prior to the plasma spray process. Cheang and Khor, 1996 reported that the plasma spray process generates a highly soluble amorphous phase along with other non-bioactive calcium phosphate phases which may cause mechanical and adhesive instability in the HA coating. Gross and Berndt, 1993 reported that the degradation of HA coatings with high amorphous phase content occurred by de-adhesion of cracked lamellae and dissolution of the remaining lamellae. However, further studies have reported that the decomposition of the apatite structure is not only sensitive to plasma spray parameters but also to the starting powder properties of the HA (Koch *et al.* 1990; Wang *et al.* 1995). Variations in the starting material in terms of size, structure morphology of the powder significantly affect the characteristics of the final coating in terms of integrity, microstructure, surface profile and degree of crystallinity.

A variety of techniques have been used to analyse HA coatings. These include atomic absorption spectroscopy, chemical analysis, infra-red spectroscopy, radiographic diffraction and scanning electron microscopy (Ducheyne *et al.* 1986; Koch *et al.* 1990; Koeneman *et al.* 1990). The events which take place at the bone-HA interface and inside the HA coating have not yet been fully elucidated.

A plasma sprayed HA coating is composed of many layers with sinus like voids interposed between successive layers (Donath, 1990). The origin of these is unknown but are possibly produced during the flame-spray technique with cooling and coagulation of the HA layers. De Lange and Donath, 1989

and Donath 1990 reported that these spaces were filled with cells, cell extensions or organic material. Bauer *et al.* 1995 described the presence of a dark staining in the outer layer of the coating, possibly representing adsorbed stained proteins.

HA has shown to undergo degradation over time (Donath 1990). This bioresorption could be due to a dissolution or a cell-mediated process (Shetty and Han, 1991; Kay, 1992). It has been shown that the higher the percentage of crystallinity of a HA coating the lower the release of calcium and phosphorous from its surface and the lower the rate of degradation (van Blitterswijk *et al.* 1993). The source of free calcium and phosphorous that is present even at the interface of highly crystalline, stable hydroxyapatite coatings appears to be the amorphous calcium-phosphate phase. This phase is found in all hydroxyapatite coatings (van Blitterswijk, 1993). It is likely that some critical amount of degradation is essential to obtain rapid biological fixation, but premature dissolution of a coating needs to be avoided. It is reasonable to suspect that if gross resorption of HA were to occur before adequate bone remodelling had developed then the mechanical stability of that implant might be compromised. Presently, a highly crystalline hydroxyapatite appears to contain adequate amounts of amorphous calcium phosphate to allow early biological fixation. This coating is also less soluble than the HA of lower crystallinity and tricalcium phosphate coatings. Fragmentation of the HA coating is a further concern as it has been suggested that these particles may migrate causing third body wear at the articulation. The excellent clinical results reported so far for HA-coated components suggest that resorption or fragmentation of the HA are not significant problems (D'Antonio *et al.* 1992; Geesink, 1993). It may be reasonable to suggest that if HA loss is associated with normal bone remodelling, then implant fixation may not be compromised. The fixation of the implant is also largely dependent upon the specific properties of the implant itself (e.g. its shape and stiffness). Implants, which, by their design, poorly transmit load to

the bone, are less likely to maintain fixation before or after HA resorption then implants of a improved design.

Several studies have investigated methods to improve the fixation of HA coated implants. These include sandwich coatings that consist of a composite of a deep layer of hydroxyapatite and a surface layer of rapidly dissolving biphasic calcium phosphates (Jaffe and Scott, 1996). Other studies have investigated new methods for the application of the HA coating, such as sputter coating or solution precipitation (Turner *et al.* 1998) which allows a uniform layer on an implant with a complex shape (Jaffe and Scott, 1996). Low-temperature precipitation processes will permit the incorporation of bioactive substances into the hydroxyapatite coating. Osteoinductive agents such as bone morphogenic protein (Horisaka *et al.* 1991; Sato *et al.* 1991) and TGF β (Beck *et al.* 1993; Lind *et al.* 1993; Kiritsy *et al.* 1993) stimulate bone formation. Antibiotics could also be adsorbed onto the hydroxyapatite coating (Shinto *et al.* 1992; Korkusuz *et al.* 1993) and released into the immediate periprosthetic area as prophylaxis against infection. A finite element analysis study has suggested that the application of the HA coating in specific patterns (e.g. stripes) in the proximal region of a hip stem could minimise proximal stress-shielding while maintaining fixation (Huiskes and van Rietbergen, 1995).

1.4 BONE ADAPTS TO ITS MECHANICAL ENVIRONMENT

For bone formation to occur, the presence of a blood supply is required as are mechanical loads. Osteoblasts function only in the immediate vicinity of blood vessels. A reduction in oxygen seems to change their gene expression and the differentiation of precursor cells more towards the formation of fibroblasts and chondrocytes (Lanyon, 1993). Secondly, the primary function of the skeleton is to carry mechanical loads that are applied either through their joint surfaces or through muscle action via tendons. It is recognised that the geometry and mass of bone are related to the types and severity of mechanical loads. Bone tissue has the capacity to adjust its mass and shape

according to the imposed strain it encounters. This appropriate match between structure and function is achieved by bone cells adapting, reinforcing, remodelling and realigning their cortical and trabecular structure. The result of this functional adaptation is that the structure matches its function with minimal bone mass. This was originally described as Wolff's Law (Wolff, transl. in 1986).

Although it is generally considered that functional adaptation is achieved by the concerted action of osteoblasts and osteoclasts (Roux, 1881), the mechanism whereby these cells are instructed for such a task remains obscure. To achieve a meaningful change of existing bone tissue, osteoblasts and osteoclasts must be regulated by local strains. Osteoblast and osteoclasts act on the surface of the tissue, while mechanical load produces displacements and strains throughout the tissue. Therefore the detection of aberrant strain may best be performed by osteocytes (Cowin *et al.* 1991; Lanyon, 1993). The sensor cells detecting the load deviations may not be the actor cells accomplishing the adaptation, as long as sensors and actors are able to communicate with one another (Parfitt, 1982). In this respect, the cellular network of bone canaliculi becomes significant (Harrigan and Hamilton, 1993). If osteocytes are the sensors of aberrant mechanical loading, they may indeed instruct osteoblasts to change their metabolic activity, either via intracellular signals such as cyclic AMP, cyclic GMP and/or ionic fluxes (such as calcium ions) (Rodan *et al.* 1975), or via extracellular signal molecules such as prostaglandins such as PGE_2 (Harell *et al.* 1977; Somjen *et al.* 1980). As osteoblasts are able to regulate the activity of osteoclasts, and thereby also modulate local bone resorption, all the cellular elements are present.

It has not yet been established how mechanical loading *in vivo* is transduced into a cellular signal. It has been known since 1984 that cells can recognise strain and that this strain can be transduced into a flux of an ion or an electrical response (Sachs, 1988). There are stretch activated ion channels in

cell membranes. The mechanism is activated when the cell membrane is strained, and a passageway of a certain size is developed for the passage of a specific ion. Ion channels have been reported in a number of different cell types including fibroblasts (Stockbridge and French, 1988) and osteoblasts (Guggino *et al.* 1989; Duncan and Misler, 1989). For more than a decade Lanyon and co-workers (Lanyon, 1984 and Rubin and Lanyon, 1984 and 1987) have been evaluating the relationship between bone tissue response and tissue-level strain magnitude in strain-gauged animal experiments using a number of species. They have shown that bone resorption will occur for tissue level strains less than about 0.001, and bone deposition will occur for tissue-level strains greater than about 0.003. Between these two tissue-level strain limits, bone tissue appears to remodel at equilibrium. If bone cells are the resorption-deposition transducers, they must be able to sense displacements of less than 100 angiostroms and emit resorption signals and sense displacements greater than 300 angiostroms and emit deposition signals. Animal experiments have shown that the magnitude, frequency and duration of loading also affect bone remodelling (Forwood and Turner, 1994, Rubin and McLeod, 1994). However, it is not known which parameters are most important: peak strain magnitude, strain distribution, threshold strain or duration of the mechanical stimulus. These studies do not explain the cellular and molecular mechanism of the response. Currently, there are two theories that may explain the cellular mechanism of the response. Transient pressures and fluid-flow is one theory and streaming potentials is the second.

1.4.1 TRANSIENT PRESSURES AND FLUID FLOW

It is generally assumed that bone cells react to strain such as fluid flow or electrical effects, but no definite experimental data has been produced on this subject. When bone is stressed, the resulting compressive strain causes the fluid pressure to rise, which in turn causes the fluid to flow to regions of lower pressure. Therefore, this fluid-flow is thought to act as the physical stimulus

to which the cells respond, rather than to the strain itself (Salzstein and Pollack, 1987; Cowin *et al.* 1991; Reich *et al.* 1990; Weinbaum *et al.* 1991).
In compact bone, axial compression of an osteon causes a radial flow of fluid from the deepest osteocytic lacunae towards the haversian channel, which is in open connection with the surrounding soft tissue (Munro and Piekarski, 1977; Piekarski and Munro, 1977; Kufahl and Salia, 1990). Thus demonstrating a convective transport mechanism that could be more significant than the diffusive transport mechanism. However, measurements (Piekarski, 1981) in the marrow of cancellous bone showed that the hydrostatic pressure reflected the pulsating character of the blood supply and not the externally-applied cyclic compressive load on the bone. Thus the hydrostatic pressure in the cortical bone pores is influenced by externally-applied cyclic compressive loads, but this is not the case for the much larger pores of cancellous bone.

1.4.2 STREAMING POTENTIALS

Bound and unbound electrical charges exist in bone tissue. At first it was thought that the signal for bone remodelling was due to the piezoelectricity of the tissue. However, more recent studies (Gross and Williams, 1982; Pollack *et al.* 1984) of the electrical effects of bone suggest that electrical potentials of electrokinetic origin dominate over those of piezoelectric origin in fluid filled bone. When fluid in channels flows due to pressure differentials between two sites in the bone tissue, the charge is convected with the fluid, giving rise to a streaming current which in turn, gives rise to a strain generated potential (SGP) (Salzstein[a] *et al.* 1987). Between the two sites there is a potential difference which can be measured. This is the streaming potential. The electrical potential is created by the flowing electrolyte when ions of one charge are attracted, or attached to the channel walls, leaving the fluid current rich in ions of the opposite charge (Gross and Williams, 1982).

A number of studies have investigated osseous streaming potentials at the microscopic structural levels (Iannacone *et al.* 1979; Pollack *et al.* 1984; Salzstein and Pollack, 1987; Petrov *et al.* 1989). It is still unclear as to the exact site where streaming potentials are generated. One possibility was that the microporosity responsible for fluid movement was the fluid space in and around mineral crystals encrusting collagen fibrils (Salzstein and Pollack, 1987; Salzstein[a] *et al.* 1987). The principle reason was because it is known that 50% of bone fluid is contained in these intercrystalline matrix spaces. However, in a recent paper (Weinbaum *et al.* 1994), it was argued that the flow of fluid was more likely to occur through the lacunar-canalicular network, since most of the water in the mineral phase of bone is bound by interaction with the ionic crystals. Significantly larger fluid spaces are found between the cell membranes of the osteocytes and the mineralised lacunar walls, as well as between the mineralised walls of osseous canaliculi and the membranes of their enclosed osteocytic cell processes.

It appears that the most likely candidate for the communication system in recognising, transmitting and transducing mechanical signals is the canalicular-lacunae system. However, it is also possible that the electrical signals pass directly through the mass of mineralised matrix to reach the bone surface, and hence this electrical signal acts directly on the cell membrane of the osteoblasts without requiring the activity of any intervening cells. This complex mechanism has yet to be elucidated.

The extent of bone's adaptive capability is as yet unknown, and the necessity for gross change in the shape of an undamaged adult bone is unusual. Both surface adaptive remodelling and internal reconstruction are at least to some extent, influenced by the bone's prevailing mechanical circumstances. Bone's mechanically adaptive capability plays an important role in orthopaedic surgery, particularly corrective treatment in young individuals, degenerative and involutional conditions in individuals of any age, and all procedures such as internal fixation or prosthetic replacement in which gross alterations are

made to the mechanical circumstances of the skeleton. However, our knowledge of the manner and extent to which mechanical circumstances influence bone remodelling is unfortunately quite small.

1.5 HYPOTHESIS AND AIMS

The hypothesis of this study is that the direct attachment and ingrowth of bone to an uncemented interface combined with implants engineered to produce interfacial strains leads to beneficial bone remodelling that may result in fixation of implants that would last a patients life-time.

The aims of the study were:

1. To investigate the uncemented implant interface under various conditions. This study aimed to investigate the conditions required for maximum bone attachment and bone ingrowth to the uncemented implant interface. This was done by examining the bony response to extra-cortical plates of different designs. By changing the geometry of these plates we were able to study the response of bone in different mechanical environments.

2. To investigate the concept of extra-cortical plates as a cementless method of fixation for bone tumour implants. The intention was to investigate whether extra-cortical plates provide a satisfactory alternative to the cemented intramedullary stem. The extra-cortical plates relied on bony ingrowth for long-term fixation and stabilisation of the implant.

The optimal conditions necessary for bone attachment and ingrowth were also investigated by altering the surface properties of the implant. The response of bone to a crystalline HA coating, a HA coating of lower crystallinity, a solution precipitated HA, a grit blasted titanium surface and a porous ingrowth surface were all examined.

Lay-out of thesis

Chapter one is a general introduction outlining cemented and uncemented implant fixation. Chapter two is an introduction to extra-cortical plate fixation. This introduction is more specific to chapters three and four where extra-cortical plate fixation has been investigated.

Chapter Two

AN INTRODUCTION TO EXTRA-CORTICAL PLATE FIXATION

Treatment using massive segmental bone tumour prostheses allows the patient to return to a near normal lifestyle. Fixation of these devices involves an intramedullary stem that is cemented into the canal of the remaining segment of bone. However, aseptic loosening of this cemented stem compromises the long-term survival of these implants. A previous study using survivorship analysis has demonstrated a 55% chance of a massive distal femoral prosthesis becoming aseptically loose after 10 years in patients under the age of 20 (Unwin *et al.* 1995). Figures for revision distal femoral replacements are even more alarming with only a 19% chance of the implant surviving after 5 years. One of the factors which contributes to the comparatively high aseptic loosening of these prostheses is that for a large majority of patients, the intramedullary stem is inserted into diaphyseal bone where there is relatively little cancellous bone available for the penetration of the acrylic cement (Oh *et al.* 1978).

A particular problem in the fixation of massive bone tumour prostheses can arise following removal of the affected bone. The amount of bone removed is different in each patient and is determined by the progression of the tumour. In some cases the segment of bone remaining following tumour resection or after revision of a failed prosthesis is small. This results in a stem that is fixed into a wide diverging canal and is surrounded by relatively weak cancellous bone. This problem is particularly evident in large distal femoral replacements where the stem is cemented into a relatively small segment of proximal femur. A study by Unwin *et al.* 1995 has demonstrated how distal femoral replacements have a higher rate of aseptic loosening when compared with other bone tumour replacements. A separate study concluded that the higher transection sites associated with distal femoral replacements results in higher bending moments at the transection site and in the cement mantle. These increased bending moments increase the incidence of prosthetic loosening (Unwin *et al.* 1996).

Retrieval of well fixed massive prostheses and their associated bone from patients of all ages shows that bone remodels to produce a neo-cortex which surrounds the cement and which is strutted off to cortex by bone trabeculae (Blunn and Wait, 1991). This is similar to that seen around cemented intramedullary stems of retrieved THR's (Malcolm, 1990). Another consistent feature seen in patients with massive prostheses is the formation of extra-cortical bone which grows up from the transection site and over the shaft of the implant.

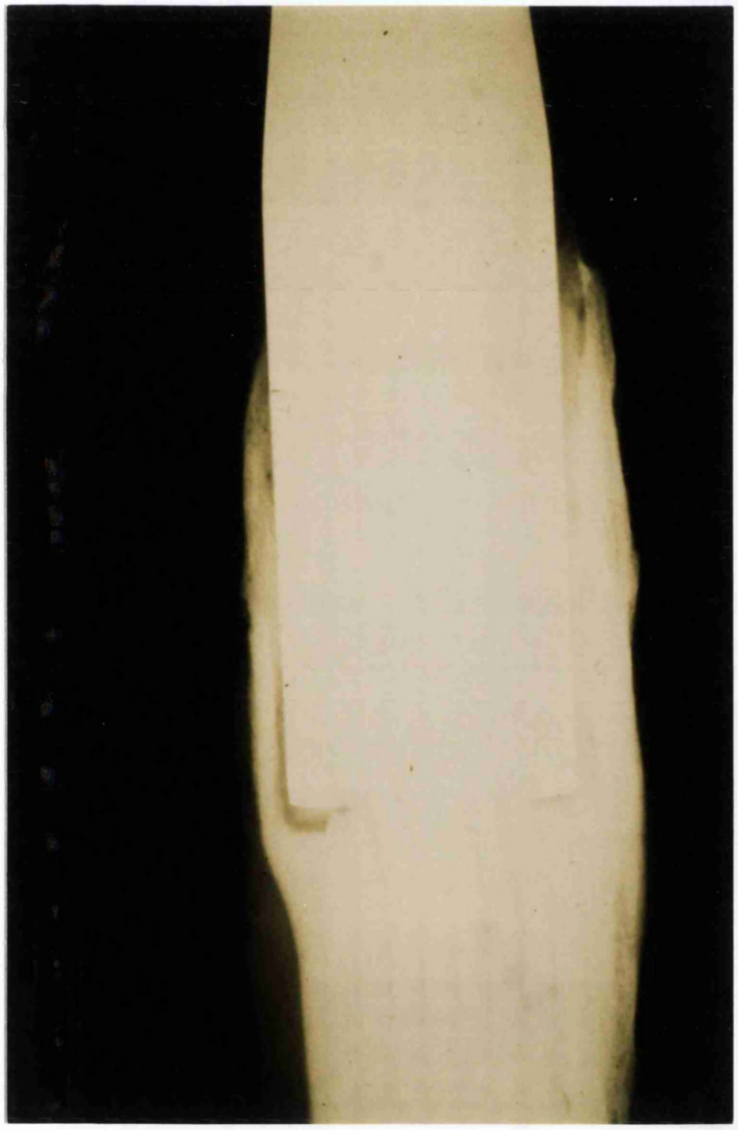


Figure 1: A photograph demonstrating extra-cortical bone formation growing from the transection site over the shaft of the implant.

Figure 2 is a histological section through this area and it demonstrates a fibrous tissue interface between the cement and bone. This interface is continuous beneath the shoulder of the implant and is seen adjacent to the shaft of the prosthesis next to the extra-cortical bone.

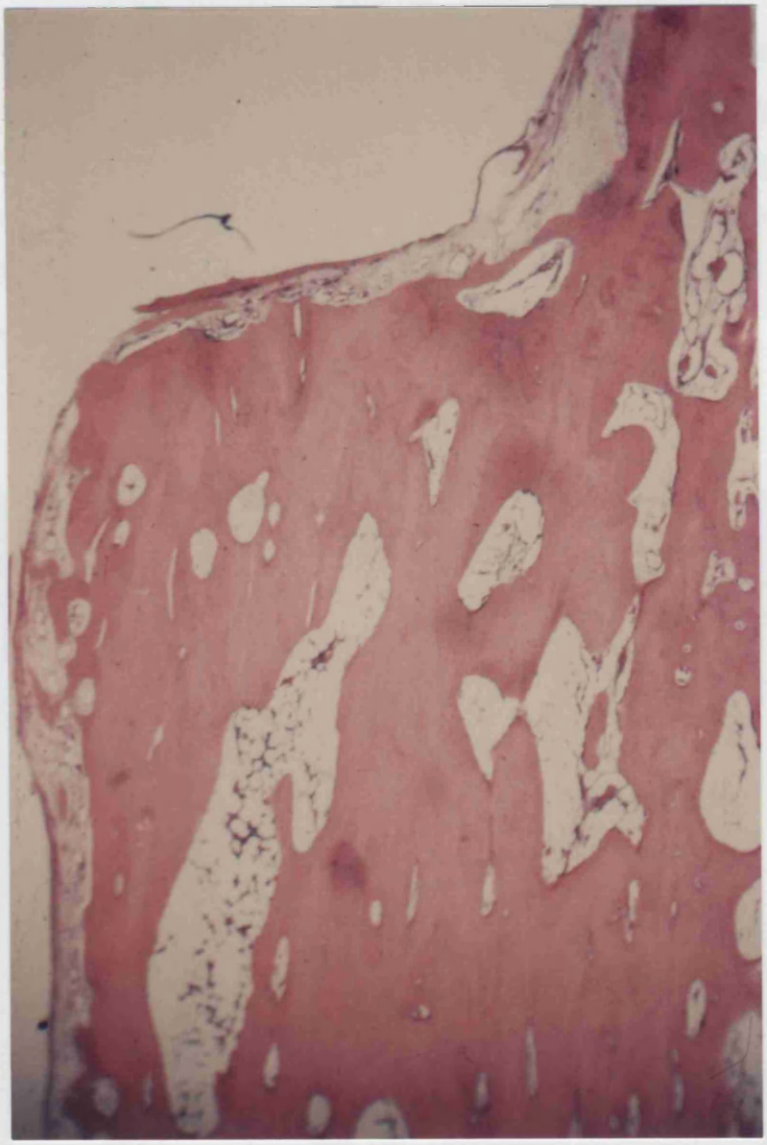


Figure 2. A longitudinal histological section demonstrating a fibrous tissue layer separating the bone and implant surface (the implant was removed during processing).

The observation of this extra-cortical bone growth led to the manufacture of "collars" on the implant adjacent to the transection site (Okada *et al.* 1988; Ward *et al.* 1993; Vieten *et al.* 1997). These "collars" were developed to encourage extra-cortical bone growth to the implant surface. It was proposed that this would enhance implant fixation. Initially, a porous beaded ingrowth collar was investigated *(fig. 3)*. However, histological examination of porous retrieved specimens showed that bone did not grow into the porous structure but was separated by a relatively thick layer of fibrous tissue *(fig. 4)*. This led to the development and implantation of a grooved hydroxyapatite (HA) coated ingrowth collar *(fig. 5)*. Figure 6 is a histological section through the hydroxyapatite-coated collar and shows how extra-cortical bone has grown into this structure.

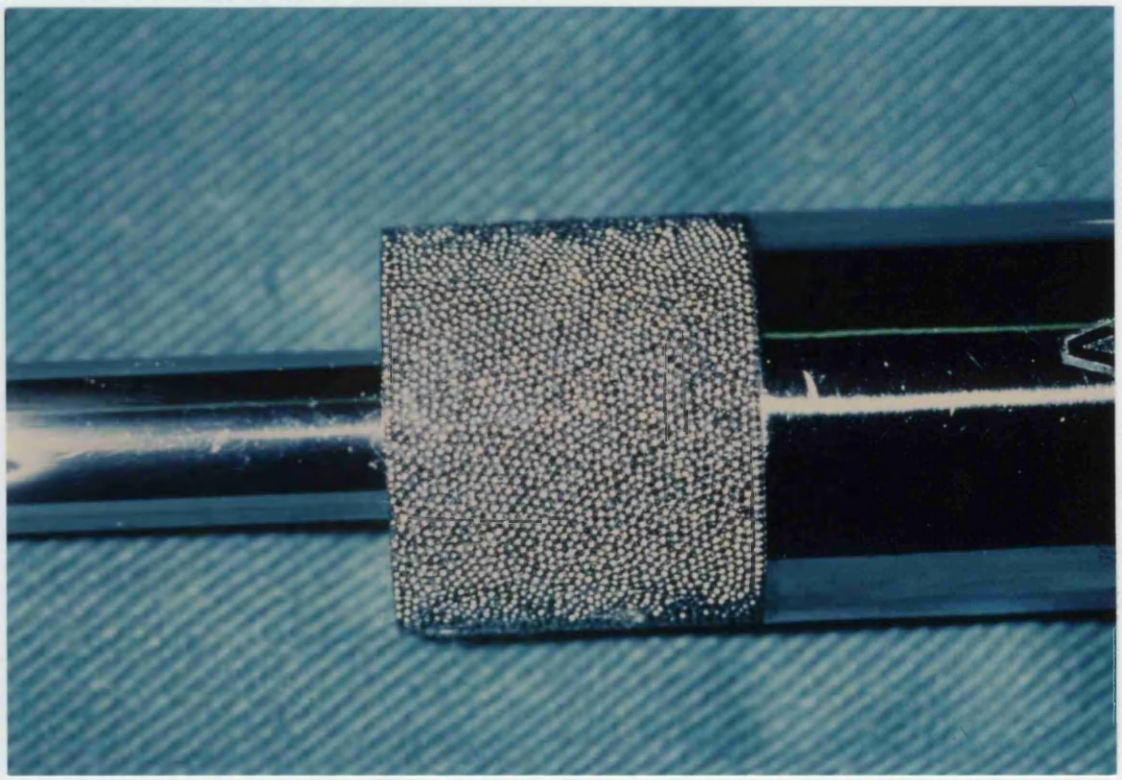


Figure 3: A photograph of a porous coating ingrowth collar positioned on the shaft of the prosthesis adjacent to the transection site.

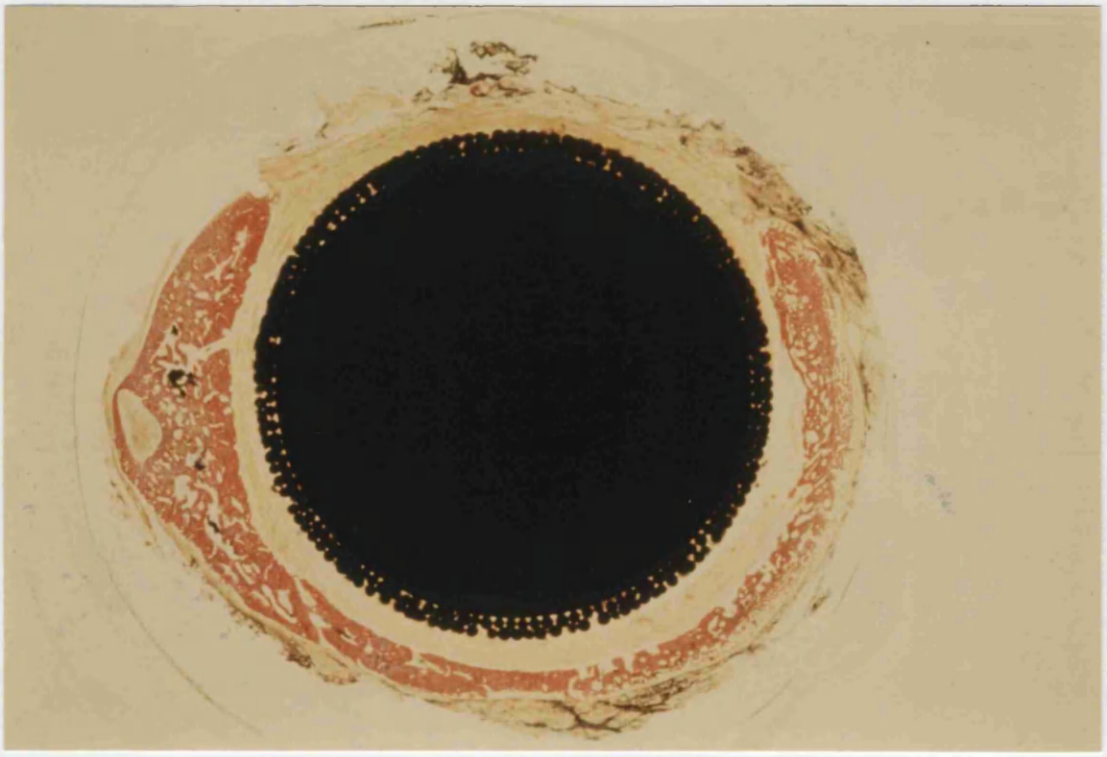


Figure 4: A transverse histological section through a porous coated collar. A fibrous tissue layer separates the bone and implant surface.

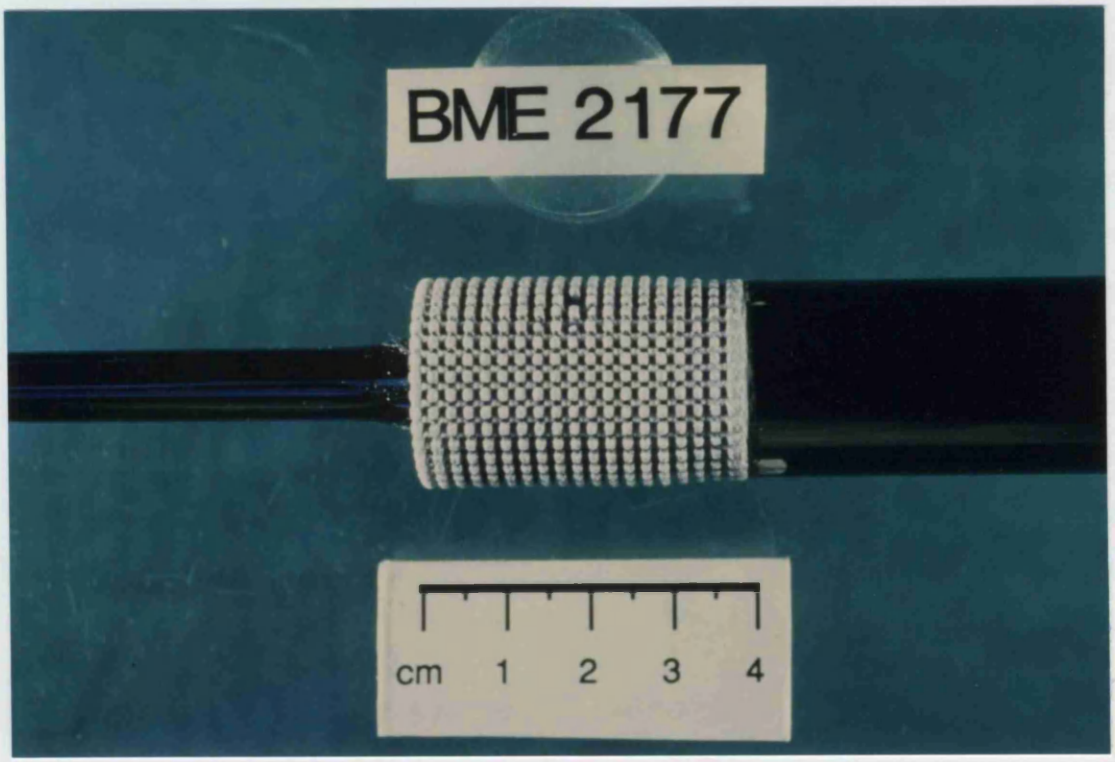


Figure 5: A photograph of a hydroxyapatite coated grooved ingrowth collar adjacent to the transection site.

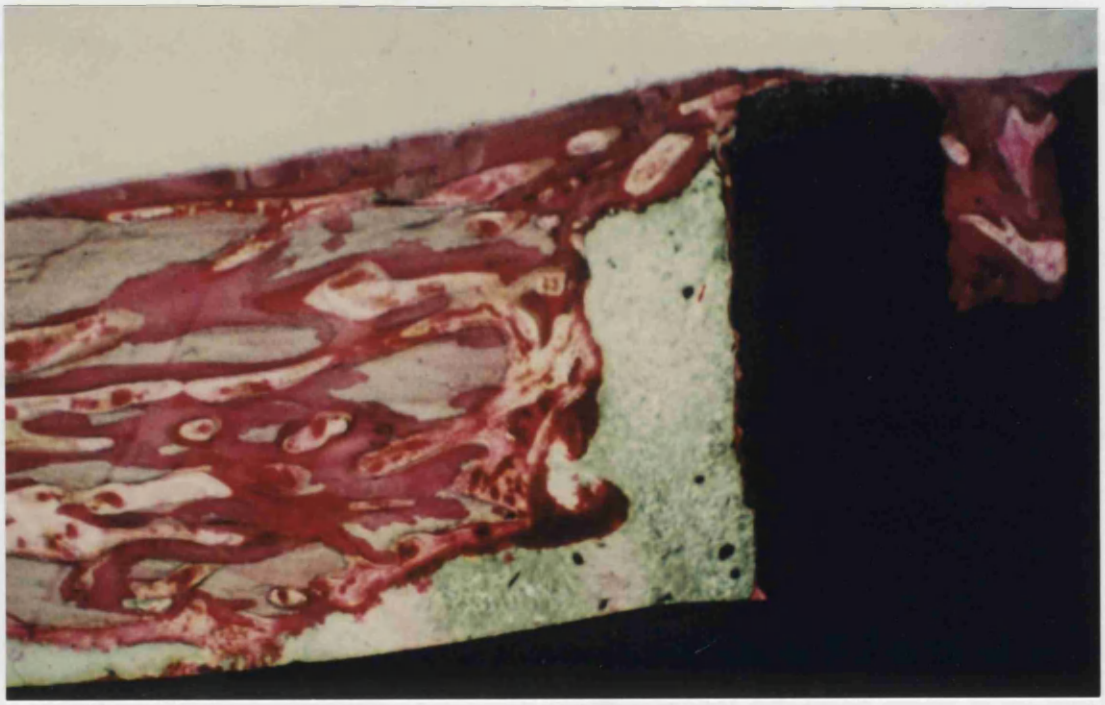


Figure 6: A longitudinal histological section through the HA grooved collar. Bone has grown into the grooves with direct bone-implant contact.

Separate studies have also investigated extra-cortical bone formation. One study reported how bone integration with the shaft of the implant reduced the development of radiolucent lines around the intramedullary cemented stem (Vieten *et al.* 1997). Another study concluded that extra-cortical bone fixation to the implant shaft reduced the amount of loading to the intramedullary stem (Taylor *et al.* 1997).

In the young, as their long bones grow, an increase in length is accompanied by remodelling and centrifugal growth. Bone formation occurs on the periosteal surface (extra-cortical formation) which results in an increase in the diameter of the intramedullary cavity (endosteal bone resorption is also occurring). This is also called cortical drift. This results in an overall increase in the diameter of bone. Remodelling continues throughout life. In the older patient a thinning of the cortex in long bones is also associated with an increase in girth.

Due to the comparatively high aseptic loosening rates of the cemented stem in bone tumour replacements and the loss of endosteal bone stock observed, extra-cortical plate fixation may be beneficial at revision surgery as it would utilise periosteal bone stock which is usually in good condition.

Therefore, in order to address the above mentioned problems associated with bone tumour replacements, and to utilise the natural occurrence of extra-cortical bone formation in both the young and old patient it would seem that extra-cortical plates would have advantages over the use of cemented intramedullary stems.

Rigid metal plates are commonly used to treat bone fractures. They are used to stabilise the fracture site, maintain good contact between bone fragments and allow early weight bearing and patient mobility. The most commonly used plate is the dynamic compression plate (DCP) which has contoured slots rather than normal round screw holes. When tightened the heads of the screws pinch the plate causing it to slide pulling the fractured surfaces together.

Many studies have reported localised cortical osteopenia under and near extra-cortical plates following fixation (Moyen *et al.* 1978; Paacolainen *et al.* 1978; Stromberg and Dalen, 1978; Slatis *et al.* 1980; Terejesen and Benum, 1983). A study by Uhthoff *et al.* 1994 demonstrated time-dependent bone loss in all three envelopes (haversian, periosteal and endosteal). The cause of bone loss beneath extra-cortical plates is often attributed to either altered cortical perfusion (Jacobs *et al.* 1981; Perren *et al.* 1988; Smith *et al.* 1990; Perren, 1991; Tepic *et al.* 1992) or stress protection of bone (Uhthoff and Dubuc, 1971; Akeson *et al.* 1976; Woo *et al.* 1976; Moyen *et al.* 1978; Uhthoff *et al.* 1981; Uhthoff and Finnegan, 1983; Uhthoff *et al.* 1993). The effect of extra-cortical plate fixation on cortical blood flow has been well documented (Gunst, 1980; Luethi *et al.* 1980; Jacobs *et al.* 1981). Perren *et*

al in 1988 reported that early cortical porosis during the first six months after plate fixation was due to interference of blood flow. This porosis was a result of removal of necrotic bone, and was followed by revascularisation and new bone formation. This early porosis was temporary and in a sheep model after the plate was removed, complete re-establishment of cortical circulation was achieved. Plates designed to reduce the amount of plate-bone contact (the limited contact dynamic compression plate (LC-DCP and the partial contact plate) have been investigated and several studies have reported that both disturbance to vascular perfusion and the degree of bone remodelling leading to a porotic cortex were decreased (Jacobs *et al.* 1981; Gautier *et al.* 1984; Perren *et al.* 1988; Perren *et al.* 1991; Tepic *et al.* 1992). These plates are used clinically (Perren *et al.* 1990; Perren, 1991). However Nunamaker *et al.* 1994 investigated cortical porosity beneath the limited contact plates and failed to show any improvement.

Many studies attribute bone loss beneath fracture fixation plates to stress shielding (Akeson[a] *et al.*1976; Moyen *et al.* 1978; Uhthoff *et al.* 1993). It has been known for some time that when physiological stress seen by bone is diminished, osteoporosis proceeds rapidly (Heaney, 1962; Hattner and McMillan, 1968; Minaire *et al.* 1974; Schock *et al.* 1975). Stress shielding occurs when two or more components with differing moduli form a united mechanical system. The component with the higher modulus bears more of the load and shields the component of lower modulus. Therefore the difference in moduli which exists between an extra-cortical plate when attached to bone results in stress transfer through the plate and shielding of load from the bone. The degree of stress shielding seen by bone is related to the rigidity of the fixation (Claes *et al.* 1982). The forces acting across the bone, as well as the stress concentrations in the bone depend on the dimensions and shape of the fixation device (Grijpma *et al.* 1992). Several *in vivo* studies have demonstrated bone loss due to stress shielding following the use of rigid internal fixation plates (Uhthoff and Dubuc, 1971; Rybicki *et al.* 1974; Woo *et al.* 1976; Tonino *et al.* 1984). The application of extra-

cortical plates to bone results in a change in the mechanical environment. These changes are represented by bony adaptations, either bone formation or resorption.

Chapter Three

THE OSSEO-MECHANICAL INDUCTION OF EXTRA-CORTICAL PLATES WITH REFERENCE TO THEIR SURFACE PROPERTIES AND GEOMETRIC DESIGN

3.1 HYPOTHESIS AND INTRODUCTION

This study hypothesised that the attachment of extra-cortical plates to the outer cortex of bone combined with bioactive surface coatings would result in the osseo-mechanical integration of the plate into the cortical structure.

Osseomechanical integration is defined as 'the incorporation of an implant into the load bearing structure of the bone such that the bone material is induced by the mechanical stresses of normal activities'.

This chapter attempted to determine the optimal geometric and surface properties required to encourage maximal amounts of bone ingrowth and attachment to extra-cortical plates. This was investigated in the rabbit model.

My study was comprised of two parts. The first part examined bone ingrowth to extra-cortical plates of various geometric designs. Percentage bone porosity in the femoral cortex adjacent to the plate was also measured to assess the quality of bone following plate fixation.

The second part of the study compared bone ingrowth and attachment to extra-cortical plates following the application of different surface coatings.

The study was directed towards developing an alternative fixation technique that would provide adequate long-term fixation and may be applied to bone tumour implants, total hips for young patients, pelvic reconstructions, and for difficult revision cases. The geometric and surface properties were investigated in order to evaluate which of these variables encouraged the maximal quantity of bone growth and attachment to an extra-cortical plate.

3.2 MATERIALS AND METHOD

Forty-eight extra-cortical plates were attached onto the left and right femora of twenty-four New Zealand White rabbits. All rabbits were 6 months of age and weighed between 3 and 5Kg. The plates were composed of titanium alloy 6Al, 4V and all measured 23mm in length and 7mm wide. Six designs *(fig. 1)* were investigated in twelve rabbits with two plates per design. All plates were curved along the longitudinal axis for an optimal fit on the femur.

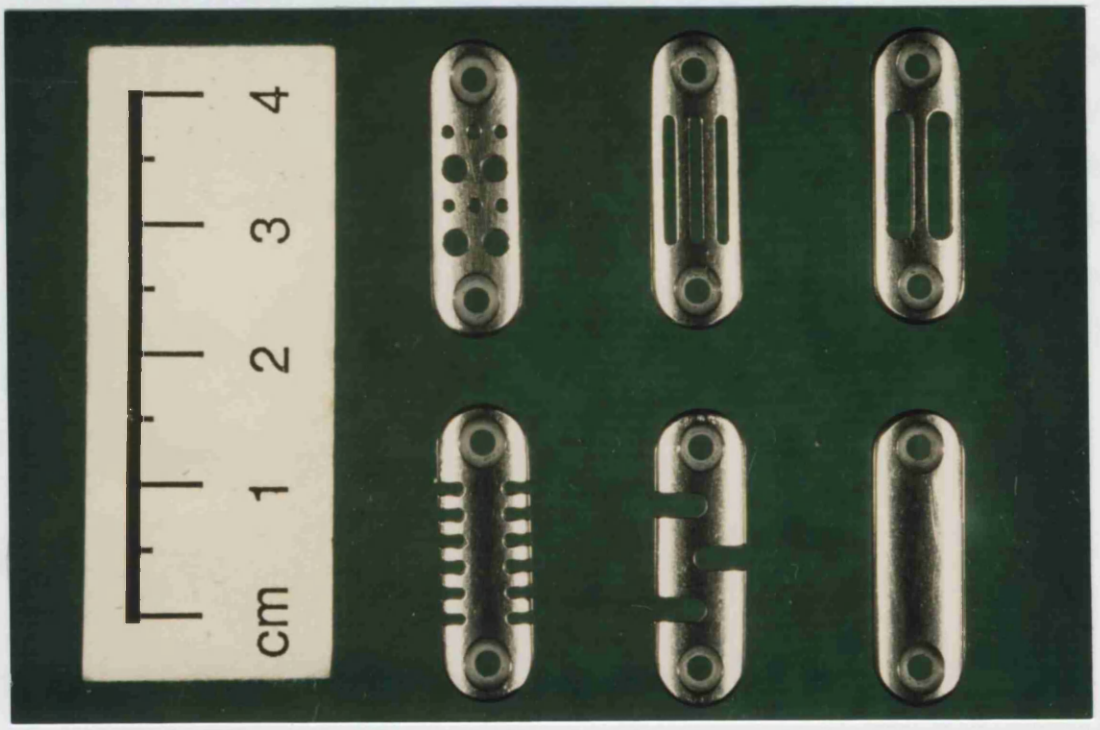


Figure 1: A photograph of the six geometric designs investigated.

The effects on bone ingrowth and attachment to four different surfaces were also compared:

1. A crystalline HA coating was compared with a roughened titanium surface in four rabbits.
2. A HA coating of lower crystallinity was compared with a crystalline HA coating in four rabbits.
3. A solution precipitated hydroxyapatite coating was compared with a crystalline HA in four rabbits.

This was a matched study with plates coated with crystalline HA implanted onto one femur whilst plates with either a surface of roughened titanium, a HA coating of lower crystallinity or the solution precipitated HA implanted on the other femur.

3.2.1 PLATE PREPARATION

3.2.1.1 CRYSTALLINE HYDROXYAPATITE

This hydroxyapatite coating was composed of a highly crystalline lattice structure (crystallinity >85%) and a 50 µm thick layer was applied onto the plate surface using the plasma spray process. All of the plasma sprayed HA coatings used in this study were developed and applied by Plasma Biotal Ltd (UK). The plasma sprayed coatings were analysed using X-ray diffraction (XRD) patterns (Division of Physics, Staffordshire University) *(fig .2)*. The crystallinity of each coating was determined by measuring the area beneath the peaks and these values were compared with a control sample.

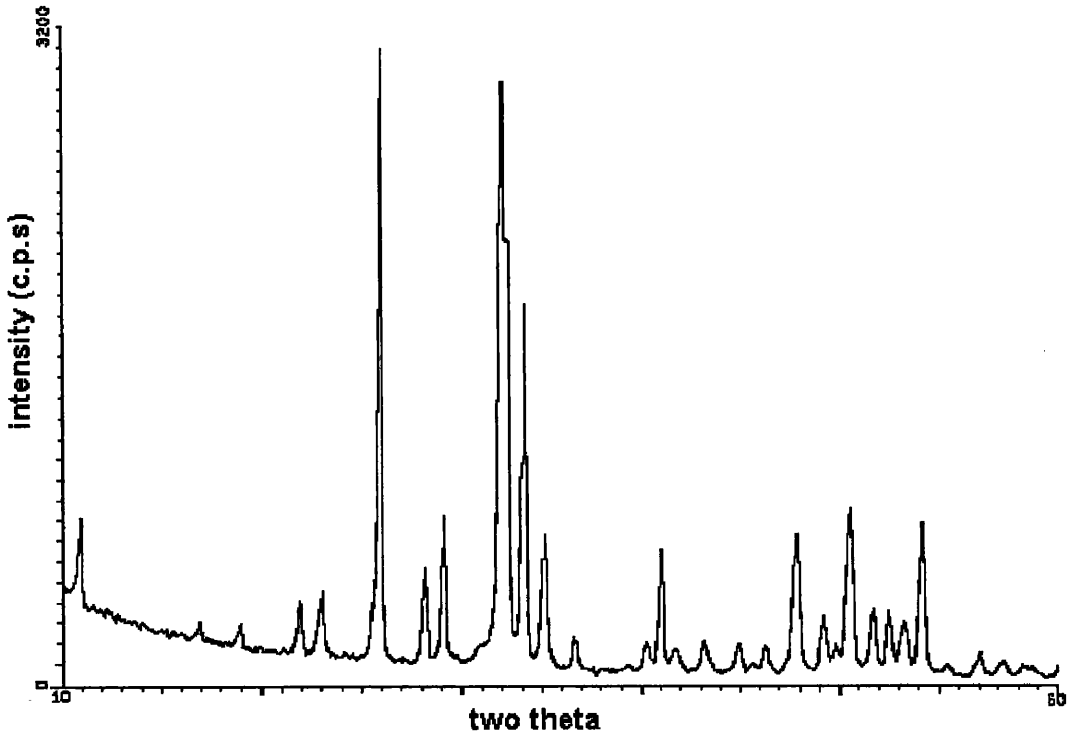


Figure 2: An XRD trace of crystalline HA.

3.2.1.2 HYDROXYAPATITE COATING OF LOWER CRYSTALLINITY

The hydroxyapatite coatings of lower crystallinity were also developed and applied by Plasma Biotal LTD (UK) *(fig. 3)*. The hydroxyapatite coating of lower crystallinity (~57%) differed from its higher crystalline counterpart due to heat treatment which had occurred prior to its application. The XRD traces demonstrated how the chemical composition of these two coatings remained similar but their physical properties differed. High temperatures catalysed the breakdown of the crystalline HA into many other forms of calcium phosphate (largely αTCP, βTCP and calcium oxide phosphate). These phosphates intermingled in the crystalline lattice structure of HA changing its shape and physical properties. This reduction in crystallinity was demonstrated by the reduction in intensity of individual peaks seen on the XRD trace *(fig. 4)*.

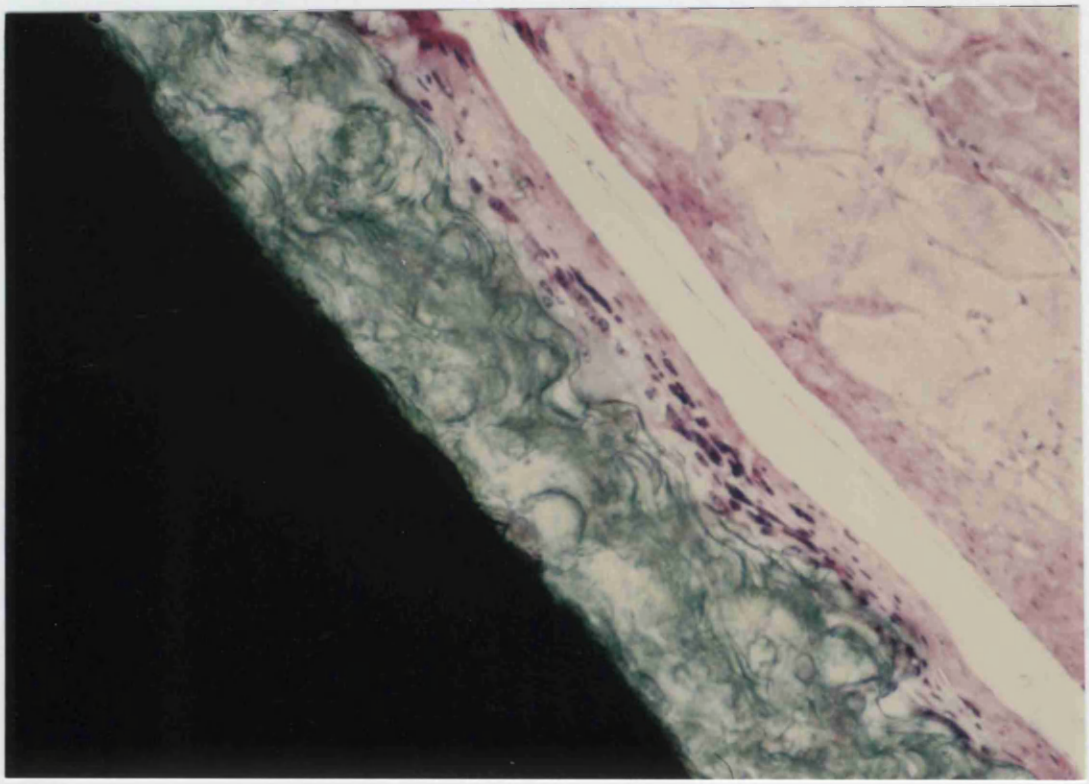


Figure 3: HA coating of lower crystallinity following application onto plate.

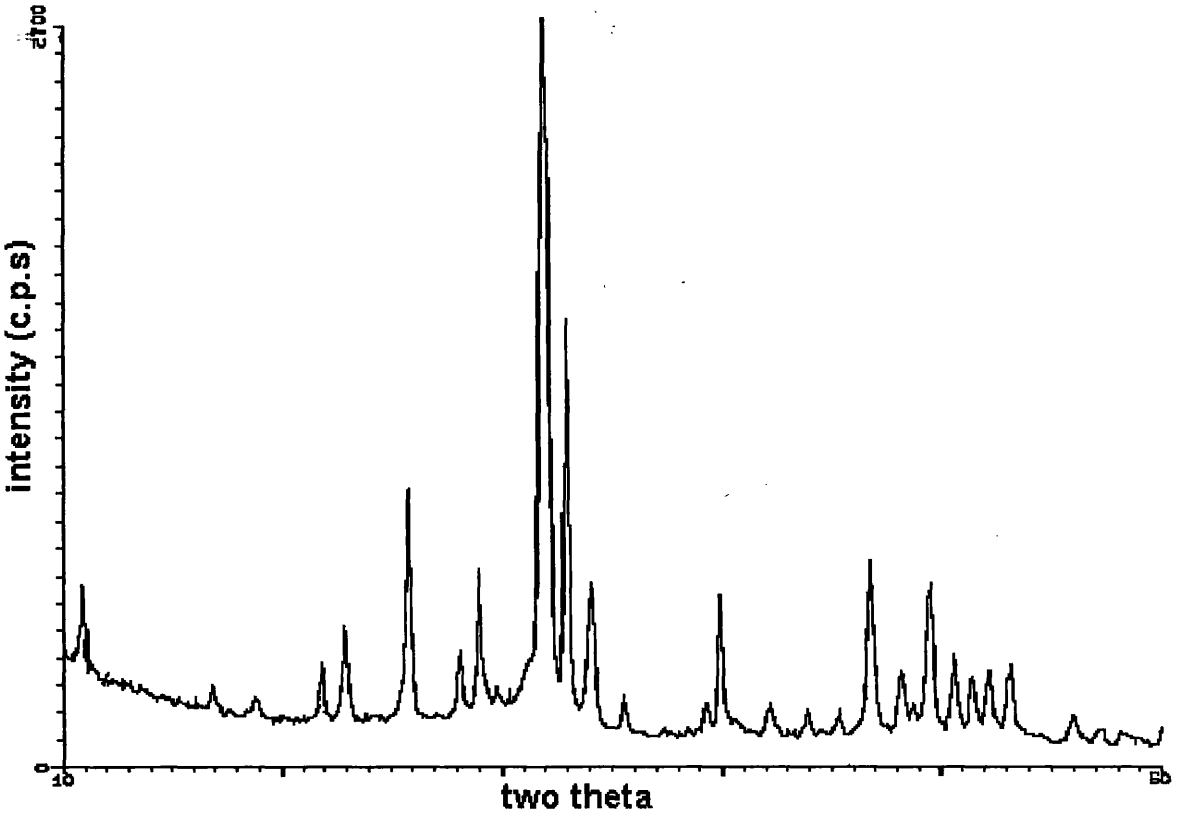


Figure 4: A XRD trace of hydroxyapatite coating of lower crystallinity.

3.2.1.3 SOLUTION PRECIPITATED HA

This HA coating was prepared and applied by Dr Blumenthal in The Hospital for Joint Disease, New York. Initially, the plates were cleaned using hydrochloric acid. This was followed by immersion in concentrated nitric acid which oxidised the implant surface. This treatment formed an oxide/hydroxide mixture on the surface of the implant which acted as a nucleating substrate. The implants were incubated in a CaP simulating fluid at room temperature which formed a tightly adherent apatite coating onto the implant surface ~5 μm thick. This coating was confirmed to be hydroxyapatite using Infra-red Spectroscopy in the multiple attenuated total reflection mode.

3.2.1.4 ROUGHENED TITANIUM SURFACE

In order to roughen the titanium surfaces, the plates were grit blasted with nylon beads which were projected from a Guyson Jetstream at 0.557 MPa producing indentations of less than 0.5 µm (6µm Ra).

3.2.2 OPERATIVE TECHNIQUE

Surgery was performed under the Scientific Procedures Act (1986). Animals were sedated via a pre-anaesthetic subcutaneous injection of Diazepam (Janssen, Animal Health, City and Eastern Chemicals Ltd. Dose 5mg/ml). This was followed by Hypnorm (Jansson, Animal Health, City and Eastern Chemicals) also administered subcutaneously at a dose of 0.4mls/kg. Anaesthesia was maintained using an oxygen and nitrous oxide mixture (1:1) and a 1 – 2% mixture of fluorothane. The muscle and fascia tissues were parted by blunt dissection and retraction. The periosteum was removed and the plate was positioned on the anterio-lateral aspect of each femur and attached by two screws located proximally and distally on the plate. The soft tissue was sutured over the plates and the wound was closed.

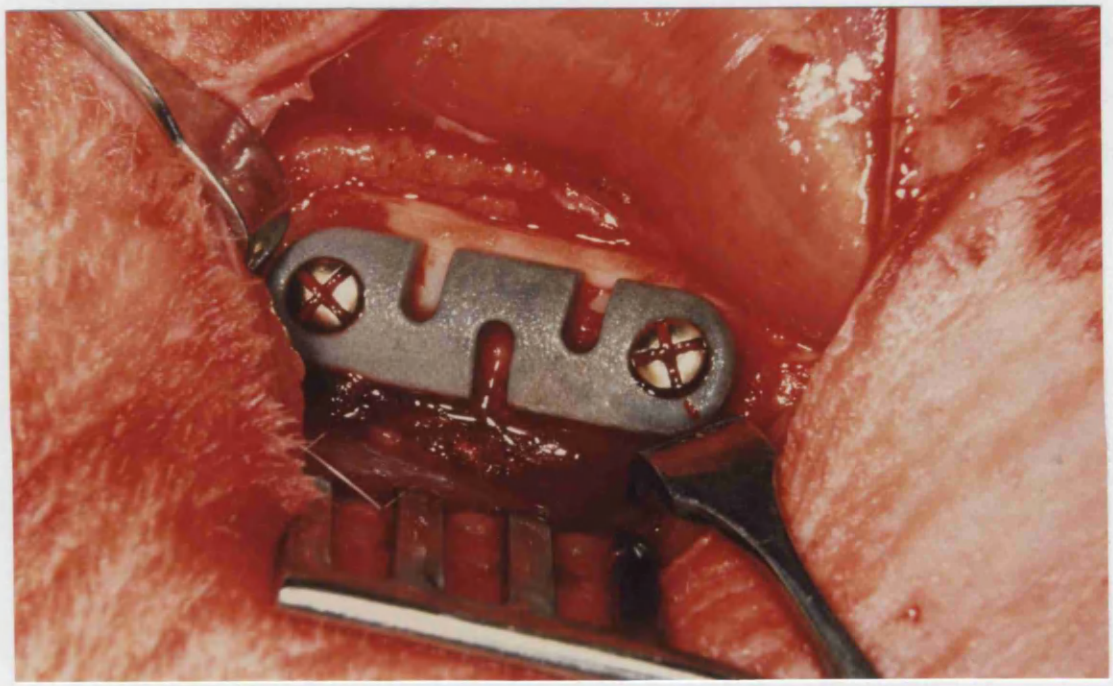


Figure 5: A peri-operative photograph demonstrating plate fixation onto the anterio-lateral aspect of the femur.

The rabbits were sacrificed 3 months post implantation following an intra-venous injection of Euthatal (Pentobarbitone Sodium. 200mg/ml. Dose 150mg/kg). On retrieval, the femora were fixed in 10% formaldehyde solution. Preparation of hard tissue sections began with dehydration of the femora in serial dilutions of alcohol (30%, 50%, 70%, 90% and absolute alcohol). This was followed by immersion in chloroform to ensure fat clearance before impregnation and casting in L R White hard grade acrylic resin. Thin sections (~50 μm) were prepared using an Isomet 2000 precision saw (Buehler Krautkramer Ltd) and a Motopol 2000 grinder and polisher (Buehler Kratkramer Ltd). Toluidine blue and Paragon were used to stain soft tissue and bone respectively.

Light microscope grid morphometry was used analyse the implant interface. The Merz graticule was developed by Merz in 1968 in response to the shortcomings associated with traditional linear square lined grids which were then used to quantify microscopic images. This method is a well-validated technique when used to quantify parameters including tissue volume, area, and when measuring tissue junction characteristics. In this study, a Merz graticule was used to quantify bone apposition on the implant surface. Bone apposition onto the four different surface coatings was measured and compared. The sites at which the Merz line (shown below) crossed the interface, determined places of measurement. At these sites, it was noted whether bone or fibrous tissue was present on the implant surface.

Four femora were investigated per surface coating. Two thin sections were made through each plate and over 40 measurements per section.

Merz graticule Points of measurement

Each of the thin sections were scanned into a Quadra 900 Apple Macintosh using a CCD colour camera. Each section was superimposed on a ruler to assist calibration and a 5mm x 10mm rectangular box into which each plate was centred. This ensured that the same area surrounding the plates was analysed. The software used to grab the image from the microscope was Neotech Image Grabber (M.E Electronics, 1988). The sections were viewed and the images manipulated (Optilab image analysis software (ME Electronics, UK)) depending on the region of interest being investigated. Fig 6a is a photograph of an image following capture from the microscope. Fig. 6b demonstrates a binary image of figure. 6a following manipulation to distinguish bone area. Particle analysis was used to quantify the regions of interest. Image analysis techniques were used to quantify total bone area, new bone growth and the percentage porosity of new bone.

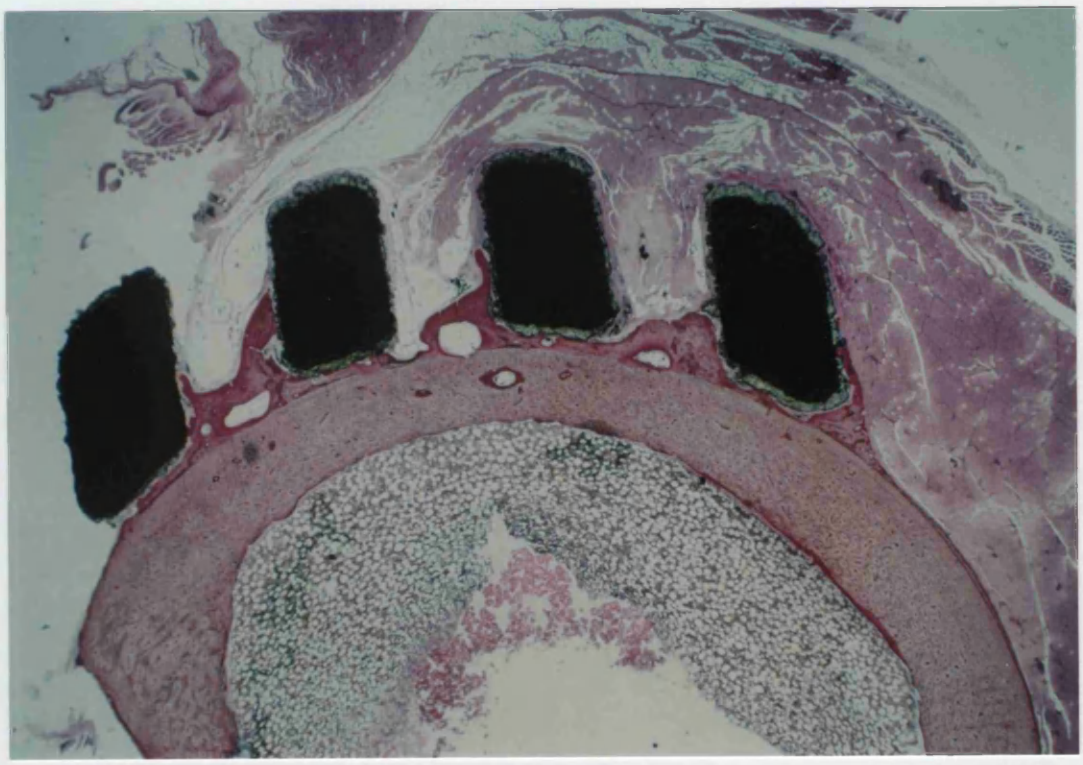


Figure 6a: A transverse histological section through the 3 vertical slot plate following image capture (Mag x1).

Figure 6b: Using Optilab software, total bone area was defined and a binary image created and measured (Mag X1).

3.2.3 STATISTICS

A normality test was used to determine whether a parametric or non-parametric test should be used to analyse the results. Values >0.05 obtained using the normality test deemed the results normal and therefore in this study the students unpaired *t*-test was used for statistical analysis where values <0.05 were classified as significant.

3.3 RESULTS

3.3.1 COMPARISON OF PLATE DESIGNS

Qualitative differences in the bony response to the plates were observed when the various designs were compared *(figs. 7a, b, c)*.

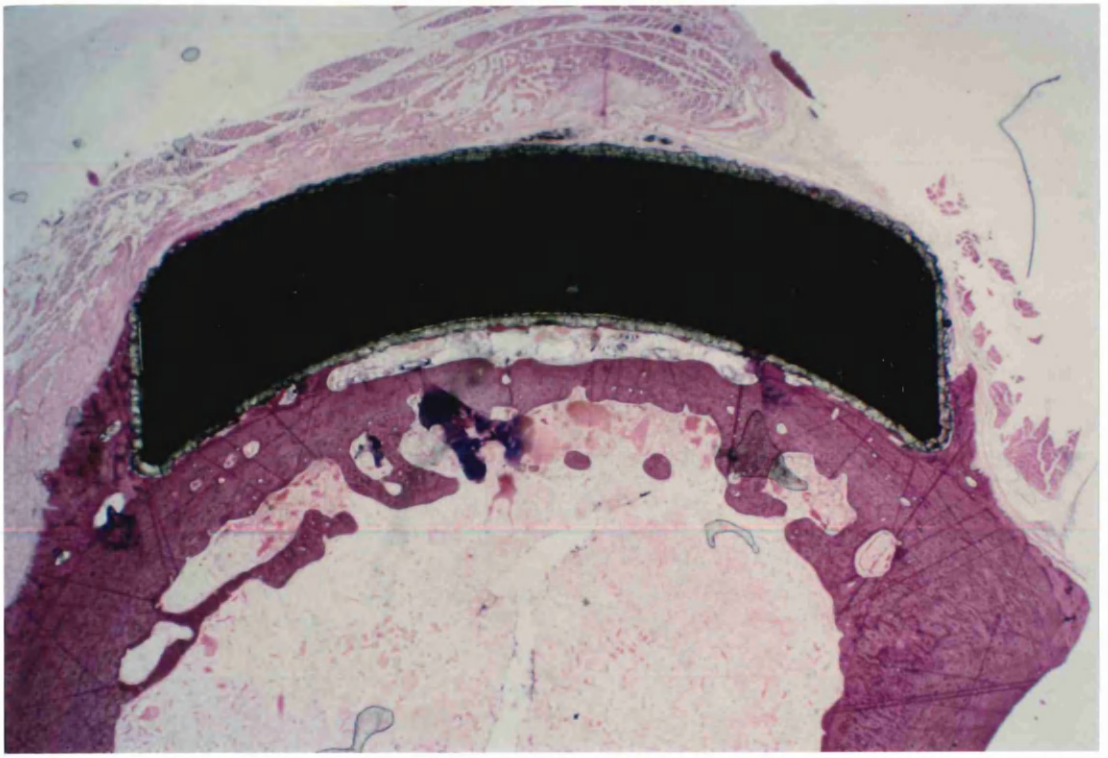


Figure 7a: A transverse histological section through the control plate design (Mag x1).

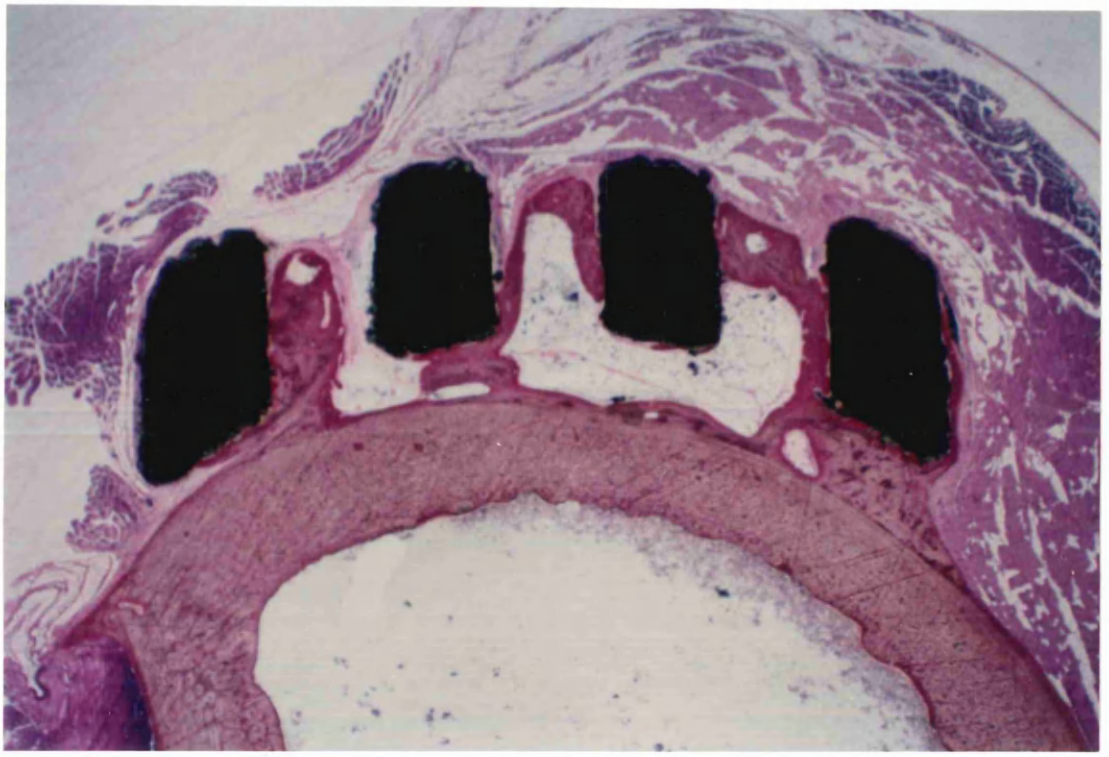


Figure 7b: A transverse *histological section through the 3 vertical slot* plate *design (Mag x1).*

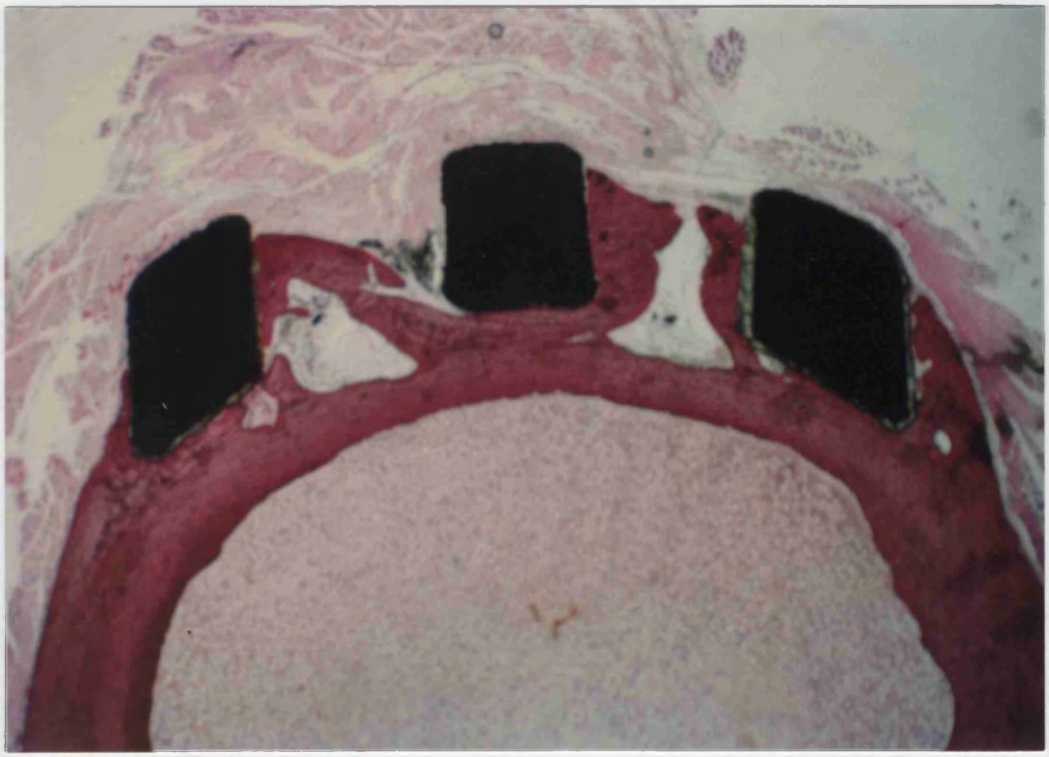


Figure 7c: A transverse histological section through the holed plate design (Mag x1).

A notable reduction in bone formation was demonstrated around the control plate and significantly more bone formation had occurred in response to the "holed" plate design when compared with the control plate ($p=0.01$). However, no other significant values were found when all of the plates were compared *(Table 1)*. Qualitative analysis showed that the larger gaps (>1mm) in the plate encouraged more bone formation when compared with the smaller gaps. Quantification of bone porosity demonstrated no significant differences when the various geometric designs were compared *(Table 2)*.

TABLE 1

P-VALUE COMPARISON OF % NEW BONE AROUND VARIOUS PLATE DESIGNS.

Control	Control	Holes	2v slots	3v slots	3s slots	12s slots
Holes	0.035					
2v slots	0.503	0.179				
3v slots	0.654	0.053	0.749			
3s slots	0.752	0.425	0.948	0.915		
12s slots	0.927	0.131	0.658	0.818	0.816	

TABLE 2

P-VALUE COMPARISON OF % POROSITY OF BONE BENEATH VARIOUS PLATE DESIGNS.

Control	Control	Holes	2v slots	3v slots	3s slots	12s slots
Holes	0.452					
2v slots	0.250	0.187				
3v slots	0.491	0.264	0.650			
3s slots	0.995	0.554	0.540	0.688		
12s slots	0.292	0.980	0.063	0.123	0.468	

3.3.2 COMPARISON OF SURFACE COATINGS

3.3.2.1 CRYSTALLINE HYDROXYAPATITE AND ROUGHENED TITANIUM SURFACE

Morphometric analysis revealed a significant increase in bone apposition ($p=0.001$) at the interface of the crystalline plasma sprayed HA coated plates when compared with the roughened titanium plates *(fig. 8)*.

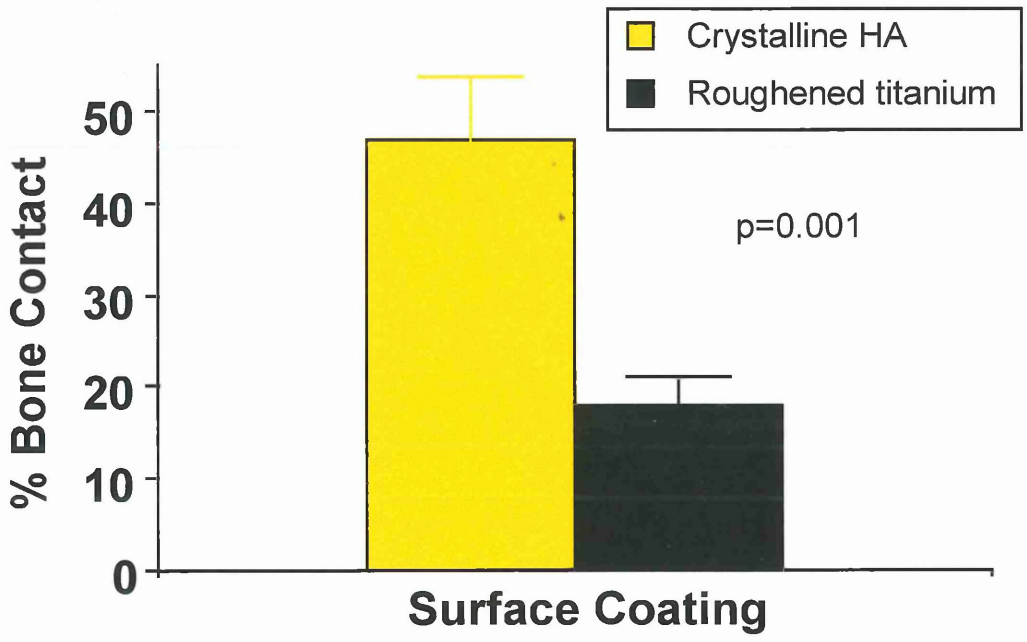


Figure 8: A comparison of bone contact onto a roughened titanium surface and crystalline HA coating.

Areas of direct bone apposition on to the crystalline HA coating was observed when viewed using the light microscope in all thin sections analysed *(fig. 9)*.

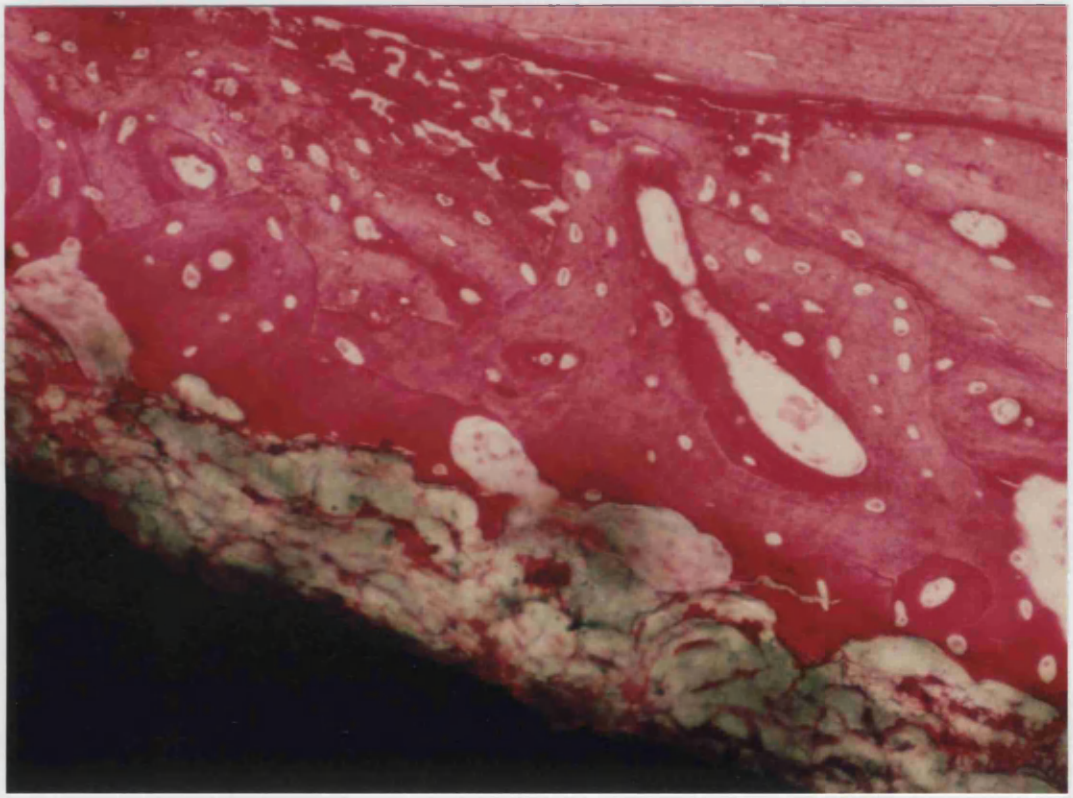


Figure 9: A photomicrograph demonstrating direct bone apposition onto the crystalline HA coating (Mag x20).

Transverse histological sections through plates with a roughened titanium surface demonstrated bone in close proximity to the implant surface but in most cases, no direct contact was observed *(fig. 10)*.

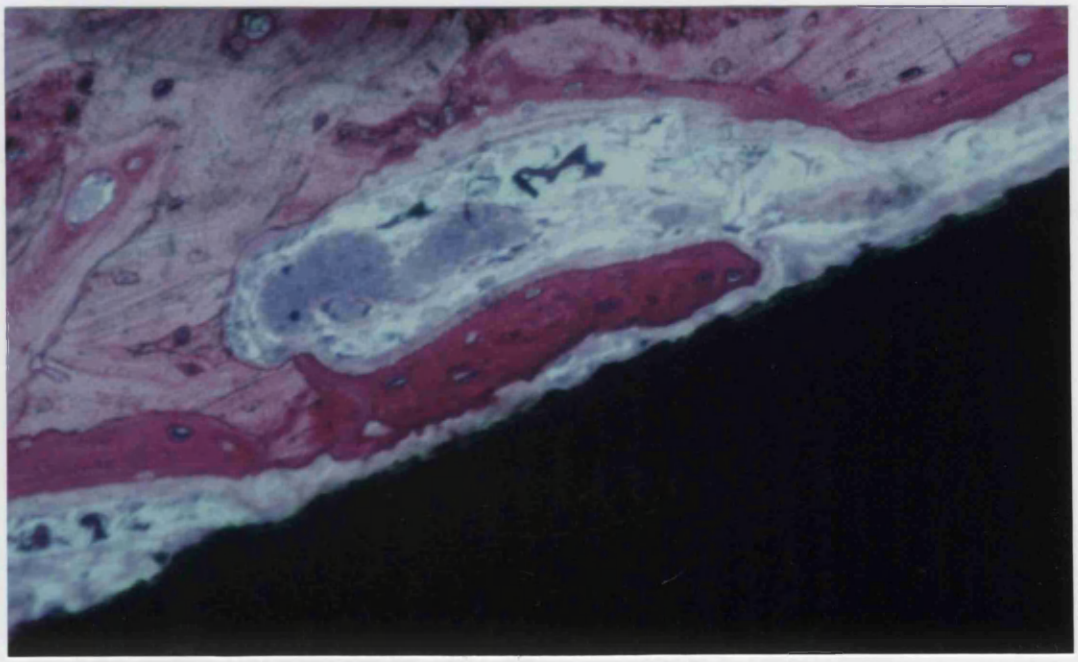


Figure 10: A photomicrograph of a histological section through a roughened titanium implant surface.

No significant difference in %new bone formation or %bone porosity was found between the roughened titanium and crystalline HA coated plates (p=0.815;p=0.425 respectively) *(figure 11 below)*.

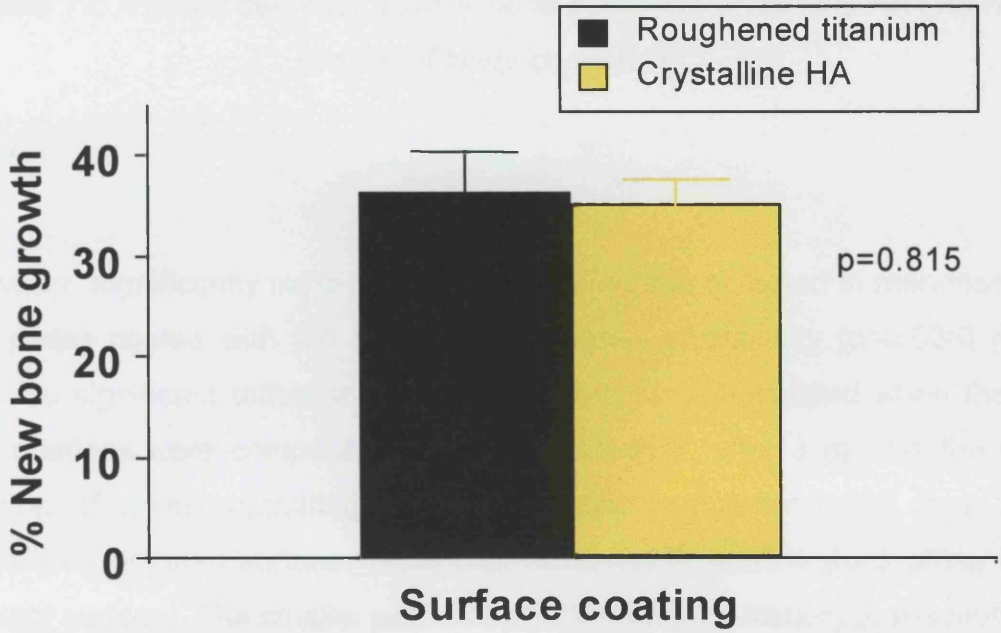


Figure 11: Graph showing % new bone growth around roughened titanium and crystalline HA coating.

3.3.2.2 CRYSTALLINE HYDROXYAPATITE AND HYDROXYAPATITE COATING OF LOWER CRYSTALLINITY

Results demonstrated significantly less bone apposition to the HA coating of lower crystallinity (p=0.004) when compared with the crystalline hydroxyapatite coated plates.

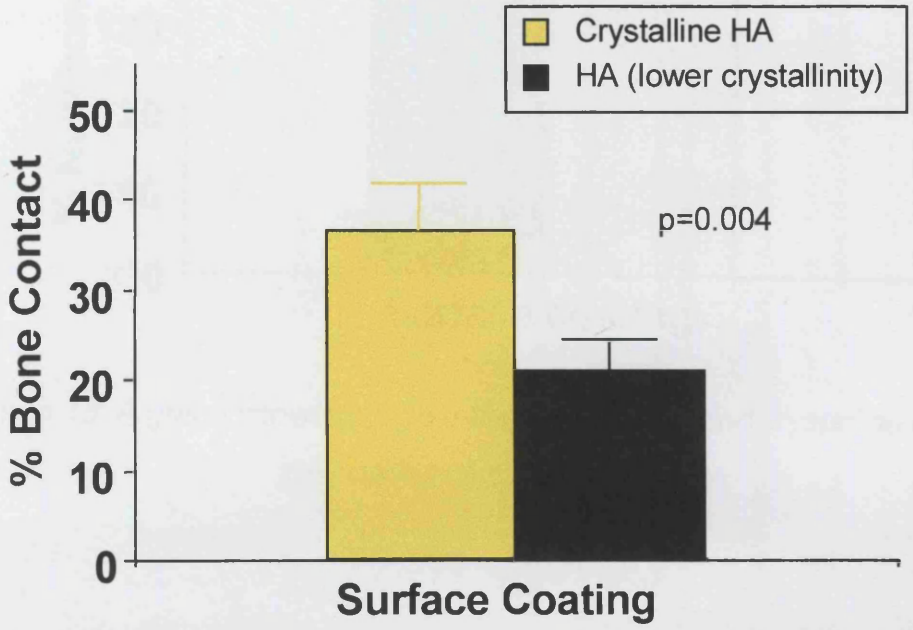


Figure 12: A graph demonstrating % bone contact to crystalline HA and HA coating of lower crystallinity.

However, significantly more new bone formation had occurred in response to the plates coated with the HA coating of lower crystallinity (p=0.036) *(fig. 13)*. No significant difference in bone porosity was calculated when these two coatings were compared (p=0.531). However, after 3 months the HA coating of lower crystallinity had fragmented and delaminated from the underlying titanium surface. This was observed in most regions along the implant surface. The smaller particles of HA induced a histiocytic reaction at the implant interface *(fig. 14)*.

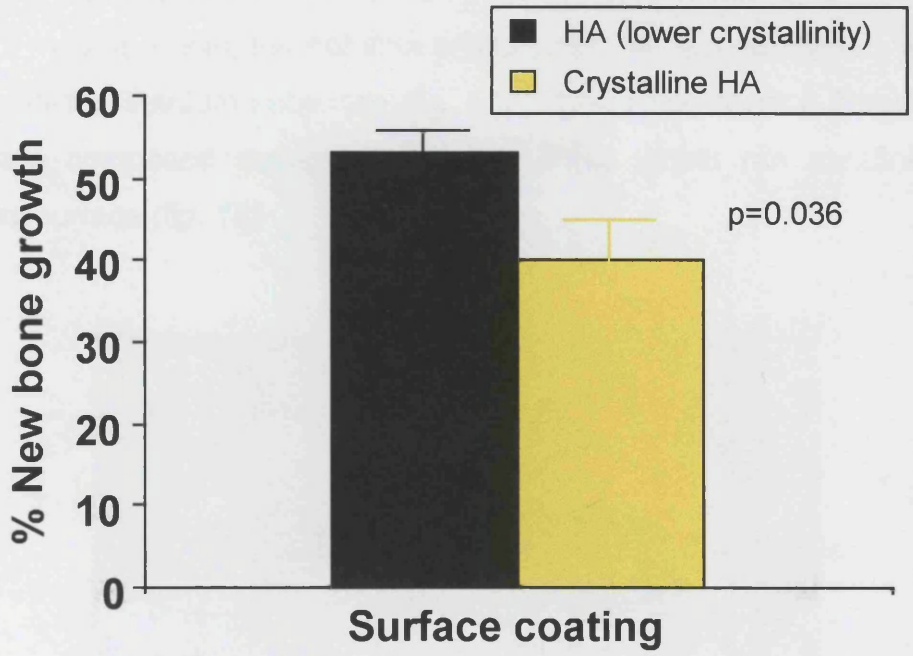


Figure 13: A graph showing % new bone growth around crystalline HA and a HA coating of lower crystallinity.

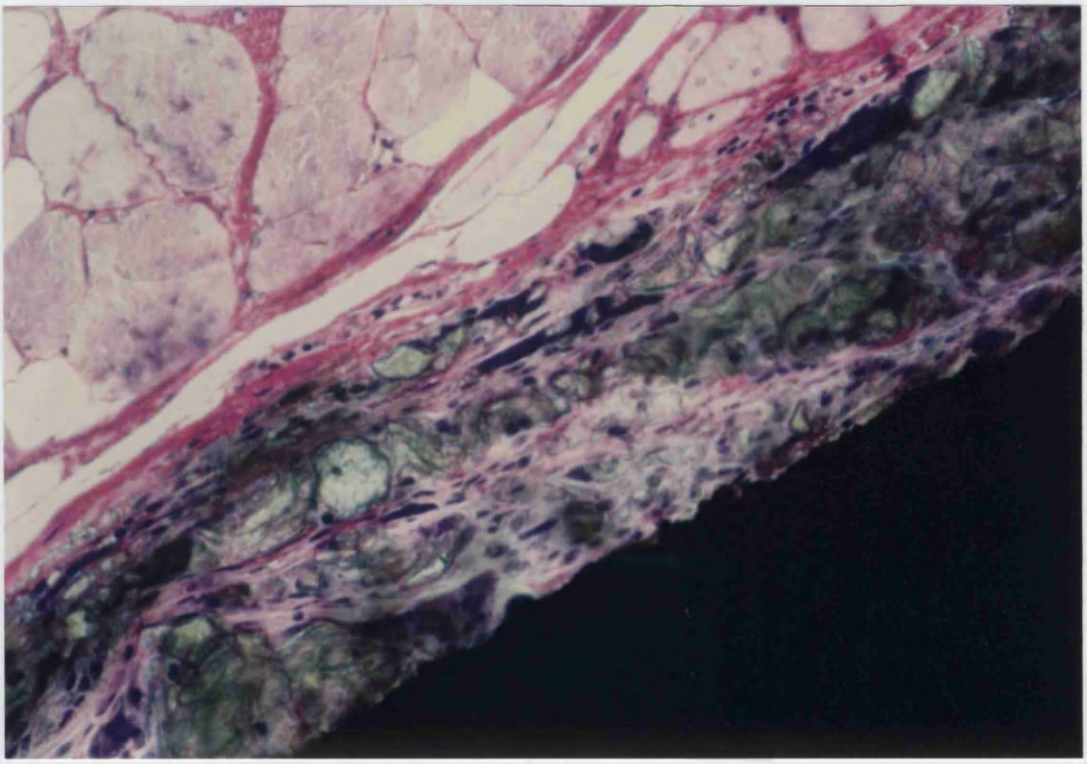


Figure 14.: A photomicrograph showing fragmentation and delamination of the HA coating of lower crystallinity (Mag x20).

3.3.2.3 SOLUTION PRECIPITATED HA AND CRYSTALLINE HA

After 3 months *in situ*, the solution precipitated HA had completely resorbed exposing the titanium substrate *(fig. 15)*. This resulted in a fibrous tissue interface composed mainly of collagen fibrils which ran parallel to the implant surface *(fig. 16)*.

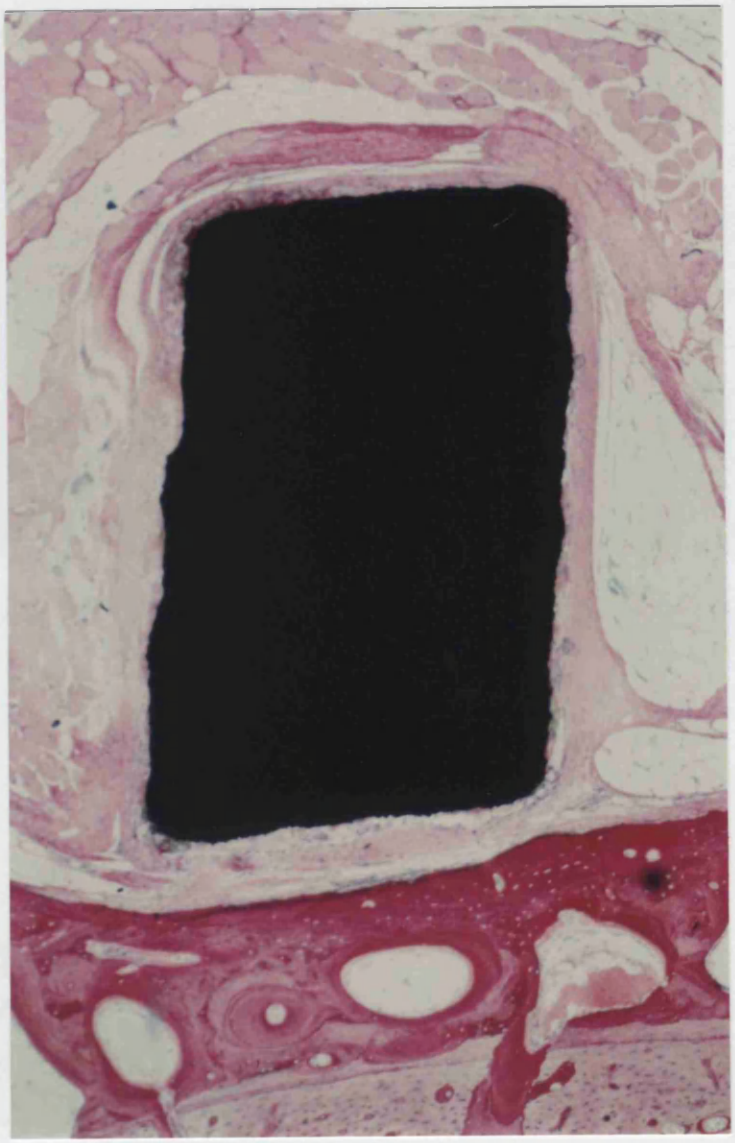


Figure 15: A photomicrograph demonstrating complete resorption of the solution precipitated HA from the implant surface (Mag x4).

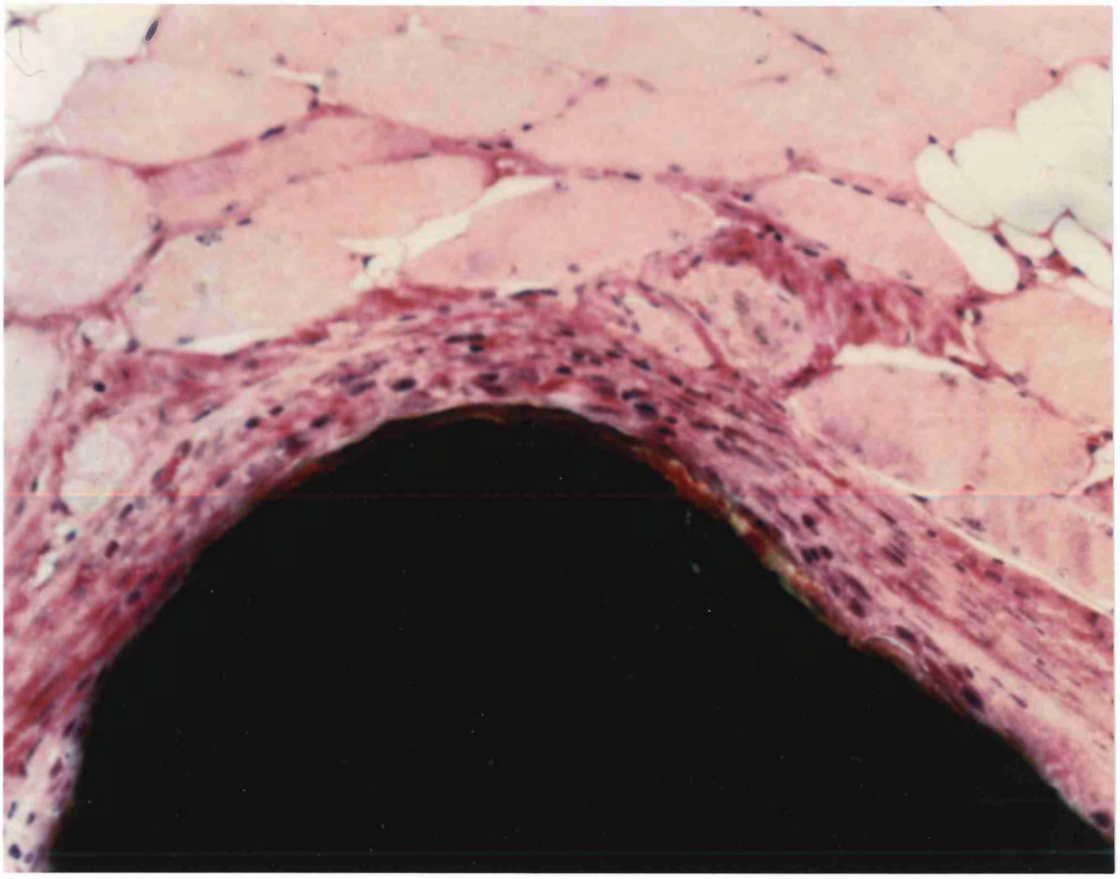


Figure 16: A photomicrograph of the implant/fibrous tissue interface following resorption of the HA coating (Mag x20).

Significantly more bone contact was measured on the surface of the plasma sprayed crystalline HA coating when compared with the solution precipitated HA coating (p=0.022) *(fig. 17)*. However, no significant values were measured when % new bone growth *(fig. 18)* and % bone porosity were compared (p=0.156; p=0.997 respectively).

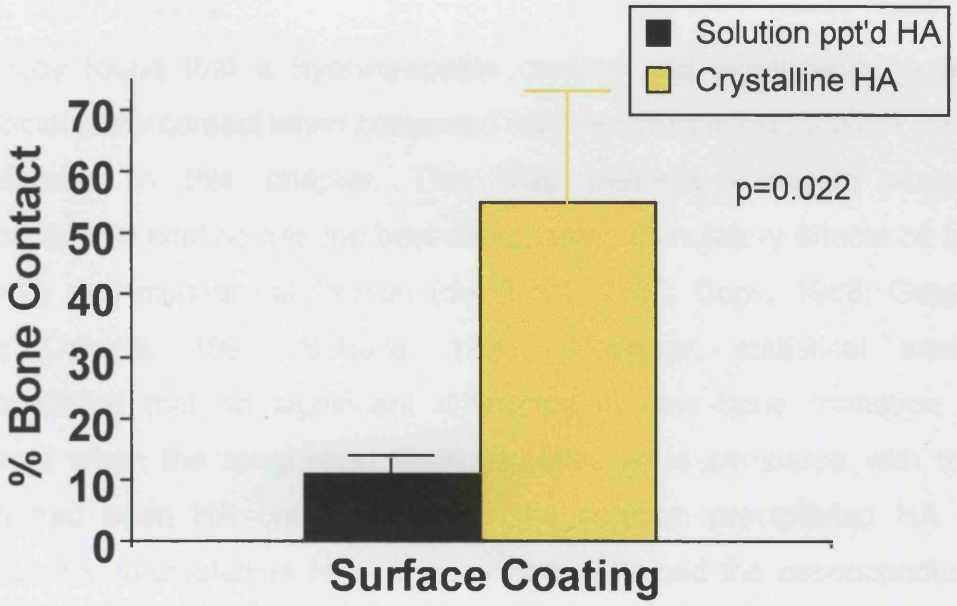


Figure 17: A comparison of % bone contact onto a solution precipitated HA coating and a plasma sprayed crystalline HA coating.

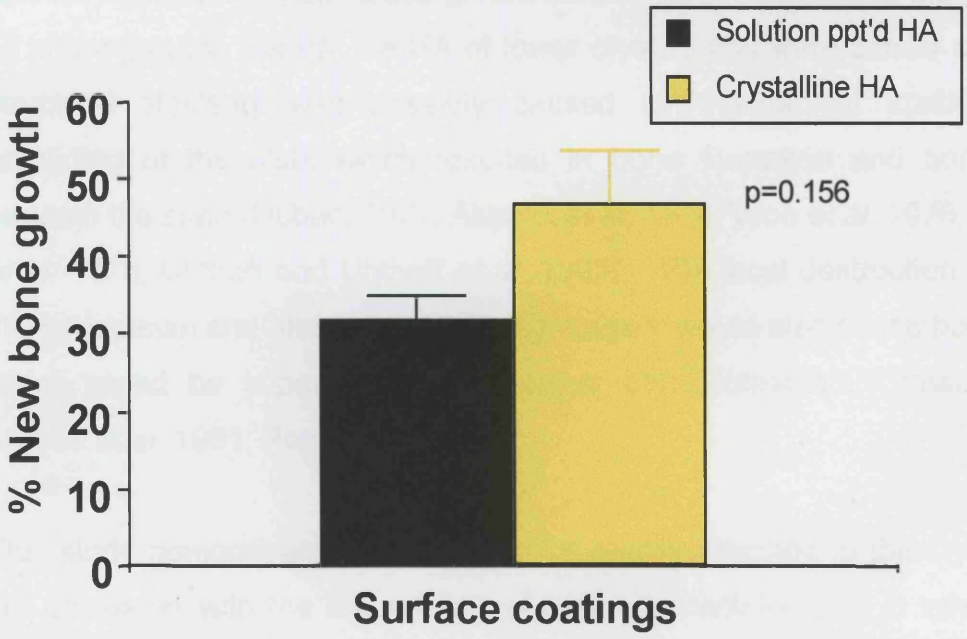


Figure 18: % New bone formation around solution precipitated and crystalline HA coated plates

3.4 DISCUSSION

My study found that a hydroxyapatite coating had significantly superior interfacial bone contact when compared with the roughened titanium surface investigated in this chapter. This was perhaps expected since a hydroxyapatite coating has the best-documented stimulatory effects on bone ingrowth and mechanical fixation (de Groot, 1987; Cook, 1988; Geesink, 1990; Oonishi, 1991; Soballe, 1993). However, statistical analysis demonstrated that no significant difference in new bone formation had occurred when the roughened titanium plates were compared with those which had been HA coated or when the solution precipitated HA was compared with crystalline HA. A study that examined the osseoconductive effects of hydroxyapatite (Geesink *et al.* 1987) demonstrated the limited and local affect that the coating had on bone. HA was shown to act on bone that lay in close proximity to the coating (<0.5mm). A possible explanation for the cortical remodelling seen in sections from all of the groups investigated may be due the mechanical stress applied on the attachment of an extra-cortical plate. The mean values of new bone area in response to the plate in all of the groups (except the HA of lower crystallinity) were similar and this structural similarity was possibly caused by mechanical loading and unloading of the plate which resulted in bone formation and bone loss beneath the plate (Dubuc, 1971; Akeson *et al.* 1976; Woo *et al.* 1976; Moyen *et al.* 1978; Uhthoff and Uhthoff *et al.* 1993). The local destruction of both the periosteum and blood supply during surgery would also cause bone loss which would be superseded by adaptive bone formation (Gunst, 1980; Jacobs *et al.* 1981; Perren *et al.* 1988).

This study demonstrated that bone more readily attached to the crystalline HA compared with the HA coating of lower crystallinity. An *in vitro* study performed by Scotchford *et al.* 1998 using primary human osteoblasts demonstrated differences in cell attachment, spreading and proliferation on plasma-sprayed HA coated surfaces of different crystallinity. They reported that a correlation existed between an increase in cell adhesion and

proliferation and an increase in the crystallinity of the HA coating. Our study also demonstrated how the HA coating of lower crystallinity had fragmented and delaminated from the titanium surface. This was not demonstrated in sections taken through implants coated with crystalline HA. This finding was in accordance with an *in vivo* study performed by van Blitterwijk *et al.* 1993 where they showed how HA coatings of higher percentage crystallinity demonstrated lower rates of HA degradation. In our study the small fragmented particles of HA provoked a histiocytic reaction at the interface of implants coated with the hydroxyapatite of lower crystallinity. This in turn reduced direct bony apposition onto the implant surface.

It has been suggested that in order for a hydroxyapatite coating to achieve biological fixation, the apatite coating must first partially dissolve in order to release calcium and phosphorus ions into the microenvironment. This allows the carbonate apatite microcrystals to associate with the organic matrix of bone (Legeros and Orly, 1991). The source of these free calcium and phosphorus ions is the amorphous calcium-phosphate phase present in all hydroxyapatite coatings (van Blitterswijk *et al.* 1993). However, HA coatings of higher crystallinity possess lower levels of this amorphous phase and this results in a decrease in the release of calcium and phosphorus from its surface (Wright, 1987). This may explain the increase in new bone growth seen adjacent to but not in direct contact with implants coated with the HA of lower crystallinity. It is also possible that as this coating had broken away from the implant surface its osseoconductive nature was acting over a wider area and therefore initiated more new bone growth in that vicinity. However, the highly crystalline HA contains adequate amorphous calcium phosphate to allow early biologic fixation to the coating.

The solution precipitated HA had completely resorbed and a fibrous soft tissue interface was seen adjacent to the titanium surface. This particular coating was in the early stages of development and there are two possible reasons why it rapidly dissolved. The first is that the thickness of the layer

applied to the implant may have been too thin. The thickness of the coating is time dependent on the length of duration of the implant in the simulating fluid. Therefore, a longer incubation time would result in a thicker coating. Another reason may be due to the solubility of the coating. By replacing the hydroxyl ions of the hydroxyapatite with fluoride ions, the solubility of the coating can be decreased. This particular coating contained no fluoride ions and so was highly soluble. This investigation observed that resorption occurred too quickly resulting in a fibrous tissue interface. However, this particular type of coating shows great promise because the manufacture and the properties of the coating are so much easier to control compared with those associated with the plasma spray process. Peri-apatite® is a solution precipitated hydroxyapatite coating produced by Howmedica, Rutherford NJ. Turner *et al.* 1998 recently reported on an *in vivo* study that examined this solution precipitated HA when coated over a three-dimensional porous ingrowth surface. They demonstrated in an ovariectomised sheep model how after 6 weeks, this HA coating significantly increased osseointegration to the implant in both osteopenic and normal bone.

When the plates of various geometric designs were compared it was found that only the "holed" design caused a significant increase in bone growth when compared with the control plate. Qualitative examination showed that the larger gaps in the plates induced more bone formation when compared with the smaller ones. Perhaps this can be explained by regenerating the periosteal blood supply and the assumption that the larger gaps in the plates expose more surface area of bone to a blood supply. A study performed by Cameron demonstrated bone growth into pore sizes ranging from 25μm up to a few millimetres in diameter (Cameron, 1994). Separate studies have reported optimal bone growth into pores ranging from 50 - 400μm in size (Bobyn *et al.* 1980; Bobyn *et al.* 1982). Cameron, 1994 concluded that the shape of the pore, whether symmetrical or irregular had no effect on the rate bone growth into that pore.

It was expected that the smaller holes and slots in the plates would induce most new bone growth because of the close proximity of the HA coating. This however, appeared not to be the case.

It can be concluded from this study that a hydroxyapatite coating is an important factor in implant fixation. Hydroxyapatite has a limited and local effect and in order to regenerate optimal quantities of bone, a combination of both the correct design and hydroxyapatite coating is required.

Chapter Four

EXTRA-CORTICAL PLATE FIXATION FOR JOINT REPLACEMENTS

4.1 HYPOTHESIS AND INTRODUCTION

Chapter three of my thesis showed that a crystalline HA coated surface provided optimal bone attachment to extra-cortical plates. The geometry did not seem to effect the amount of bony remodelling but slots in the plate did appear to be beneficial as bone formation occurred within the slots. For this reason, slotted HA coated extra-cortical plates were selected for use to anchor a midshaft tibial replacement in a goat animal model.

The hypothesis for this part of the investigation was that by using prostheses that alter local stresses in cortical bone combined with a coating which encourages bone integration, remodelling would securely anchor the extra-cortical plates to bone. The aim of this study was to investigate whether extra-cortical plate fixation was reliable. A second aim was to investigate how bone remodelled around extra-cortical plates and to discover if this remodelling was related to the stresses in the bone and the rigidity of the implant.

In this study, mid-shaft tibial replacements were fixed using hydroxyapatite coated extra-cortical plates attached by trans-cortical bone screws to the outer cortex of goat tibiae. The implants used in this study were designed to replicate the conditions surrounding massive segmental bone tumour replacements. These plates relied on the induction of extra-cortical bone formation into and around the plates to secure the implant to bone. Extra-cortical plate fixation specifically addresses the problems associated with the fixation of primary and revision massive implants and the fixation of these prostheses into the remaining short segments of bone. This type of implant may also be suitable where periosteal bone formation occurs naturally, such as in the growing patient. There may be more applications for extra-cortical plate fixation, for example, in revision THR where endosteal bone stock has been compromised.

4.2 MATERIALS AND METHOD

Fourteen individualised mid-shaft prostheses were inserted into the right tibia of adult female goats aged between 2 - 4 years. Of these, 9 implants were implanted for 6 months. In order to investigate early bone remodelling around these prostheses five implants were removed after 2 - 14 weeks. All of the prostheses were composed of two parts that were joined together at surgery by two juxta-positioned screws located centrally in the shaft. Of the prostheses inserted for 6 months, three implants were fixed proximally to the bone using two extra-cortical plates, three were fixed using three extra-cortical plates and three were fixed using six extra-cortical plates shown below (fig.1).

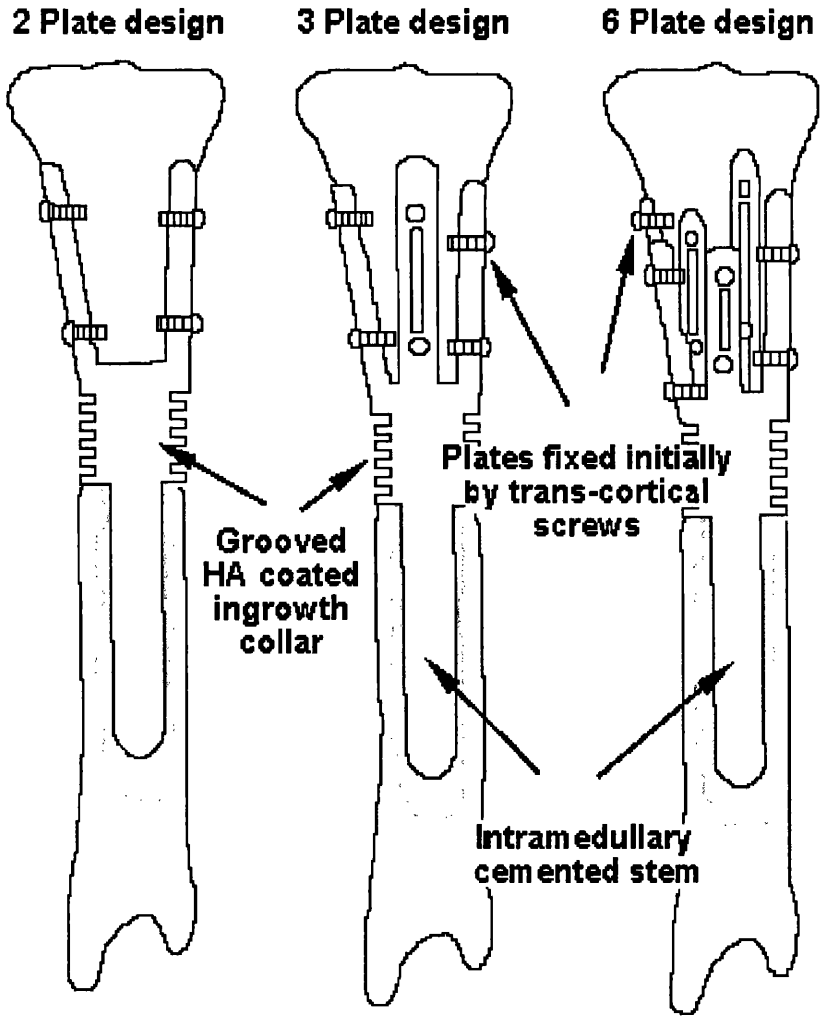


Fig.1: A schematic diagram of the 3 implant designs investigated.

The 2 and 3 extra-cortical plate designs were attached to the outer cortex of the tibia via two 14mm X 4.5mm trans-cortical bone screws located proximally and distally on the plates. Due to the smaller size in width of the 6 extra-cortical plate design the screws used measured 6mm X 2.4mm. The stiffness of the plates was a variable factor. All of the implants were fixed distally by a cemented intramedullary stem. A grooved HA coated ingrowth collar was located at the shoulder of the implant adjacent to the cemented stem.

A highly crystalline (>85%) thin (<75μm) hydroxyapatite (HA) coating was applied to the surface of the segmental portion of the implant and to the inside and outside of the extra-cortical plates using a plasma spray process (Plasma Biotal Ltd, UK). Composition and purity of the coating was confirmed using X-ray diffraction (Department of Physics, Staffordshire University) *(fig. 2)*. The crystallinity of each coating was determined by measuring the area beneath the peaks. The values were then compared with a control sample.

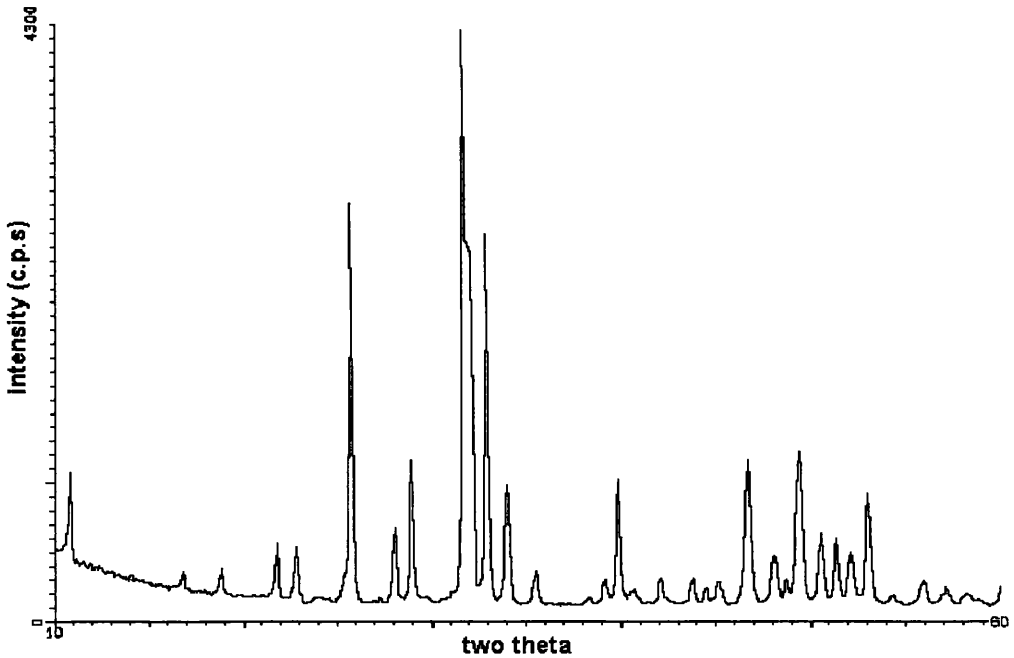


Figure 2. An XRD trace of crystalline hydroxyapatite.

4.2.1 OPERATIVE TECHNIQUE

All procedures were carried out and regulated by the Scientific Procedures Act (1986). All animals were housed in an indoor pen two weeks prior to surgery and starved for 12 hours. Pre-operative anaesthesia was induced with an intramuscular injection of Xylazine (Rompun 2% 0.005ml/kg; 20mg/ml. Bayer AG Leverkusen) followed by a slow intravenous administration of ketamine (Vetalar 100mg/ml; Pharmacia and Upjohn Ltd 0.02mg/kg). This was followed by intubation and an oxygen (2 litres/min) and halothane (1.5 - 2%) mixture was used to maintain anaesthesia. During surgery the goat was placed in the right lateral recumbancy in order to gain exposure to the right tibia. A medial incision was made which measured approximately 10cm and was located over the shaft of the tibia. Several fascia layers were cut, the periosteum lifted and the tibia exposed. Osteotomy was achieved using a sagittal air saw. Frictional heat generated was cooled using sterile isotonic saline. A 50mm segment of bone was removed and the prosthesis inserted. Palacos (with Gentamycin) low viscosity bone cement was used to stabilise the intramedullary stem in the distal segment of bone. Following drilling and tapping for screw placement, the extra-cortical plates were attached onto the proximal segment of tibia. The two halves of the prosthesis were joined and the periosteum sutured in place around the implant. The fascia and skin layers were then sutured.

Antibiotic and analgesic prophylaxis was administered daily with subcutaneous injections of Baytril (Enrofloxacin 5mg/kg; Bayer AG Leverkusen) and Finadyne (Flunixin Meglumine 2mg/45kg; Schering-Plough Ltd) for three days post-surgery. Immediate post-operative mobilisation and weight bearing was allowed, as tolerated by the goat. The clinical function of the operated tibia was evaluated subjectively by observing the animal's activities such as weight bearing, walking and the ability to browse and stand on hind limbs.

Fluorescein bone markers were used to quantify bone remodelling around the different prosthetic designs. The uptake of tetracyclines at sites of bone mineral deposition provided a means of demonstrating regions of active bone formation and mineralisation. Oxytetracycline (15mg/kg) and demethylchlortetracycline (20mg/kg) rapidly localised at these sites, so that they appeared as bright yellow and orange fluorescent lines respectively when observed in undecalcified thin sections under UV light. An alternate dose of each marker was administered by subcutaneous injection at intervals of two months. This provided a method for the estimation of the rate of bone remodelling. The measurable distances between the cement lines of tetracycline uptake indicated the amount of bone deposited in the interval between the doses. Bone in the proximity of unslotted plates and bone development around slotted plates were compared with bone formation rates observed in normal cortical bone.

On retrieval both the left and right tibiae were removed and fixed in 10% formaldehyde solution. Soft tissues were removed and each specimen radiographed. The unoperated and operated tibiae were cut into 5mm transverse slices using an Exotom cut off machine (Struers, UK). Tibiae were cut in the same regions such that the operated and unoperated and 2, 3 and 6 plate designs could be compared. Again, all slices were radiographed. Preparation of hard tissue sections began with dehydration of the sections in serial dilutions of alcohol (30%, 50%, 70%, 90% and absolute alcohol). Alcohol-ether (50:50) was used for fat clearance and this was followed by impregnation and casting in LR White hard grade acrylic resin. Thin sections (<50 μm) were prepared from each 5mm slice using an Isomet 2000 precision saw (Buehler Krautkramer) and a Motopol 2000 grinder and polisher (Buehler Krautkramer). Toluidine blue and Paragon were used to stain the soft tissue and bone respectively.

4.2.2 IMAGE ANALYSIS

Each of the thin sections were image captured (Neotech Image grabber; M.E electronics, 1989) into a 900 Quadra Apple Macintosh using a CCD colour camera. The sections were superimposed on a ruler for calibration. The viewed images were manipulated to distinguish bone area or porosity using image analysis software (Optilab, Graftek, 1988). A binary image of the selected region was generated and then measured using particle analysis *(fig.3)*. In all cases, total bone area and cortical porosity in the proximal, mid and distal regions of the plated tibiae were measured and compared with regions on the contralateral unoperated limb. Total bone area and porosity were also compared between the three different implant designs.

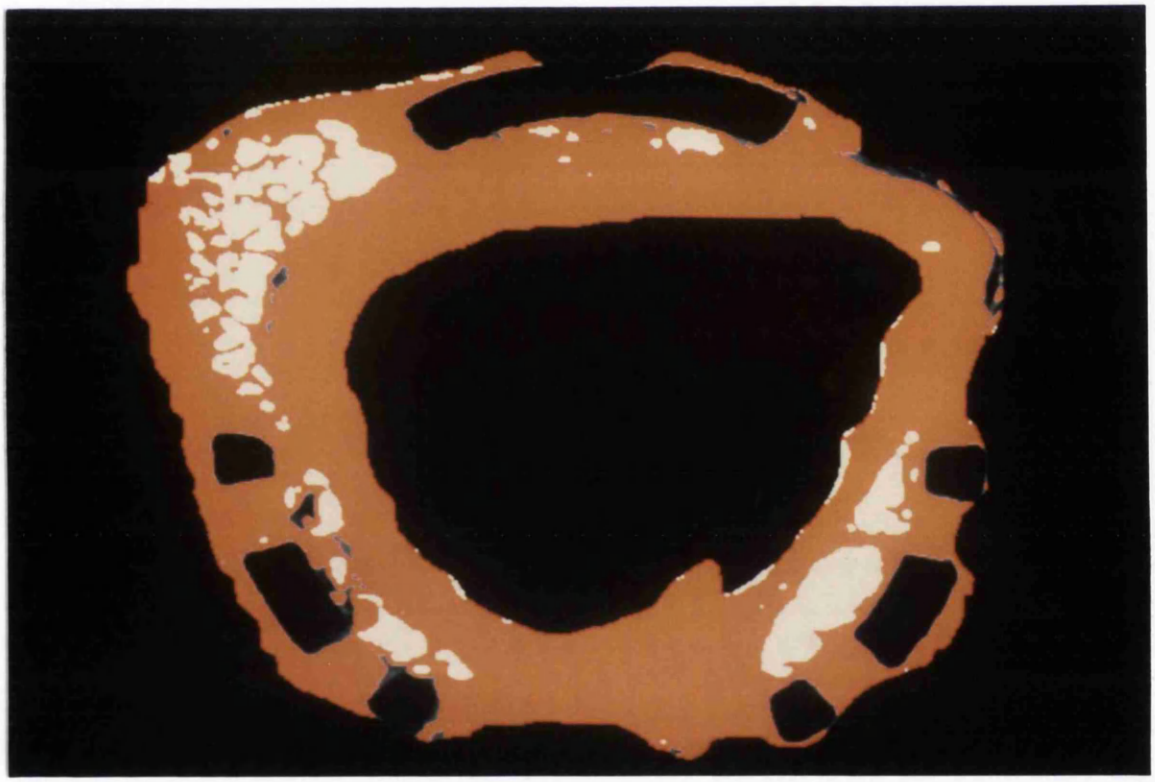


Figure 3: A photograph demonstrating how total bone area has been selected and a binary image generated from a transverse section through the 3 plated implant design.

4.2.3 FINITE ELEMENT ANALYSIS

Finite element analysis was used to examine the mechanical significance of extra-cortical plate fixation to bone. FE analysis measured the moment of inertia of an area (I) from each cross-sectional area of bone in the A/P and M/L planes. The moment of inertia of an area is a measure of the distribution of a material in a certain manner about its centroid. This distribution determines its rigidity in bending. The unit of measure is meters to the fourth power. The moment of inertia of an area allowed the analysis of bone under different bending and torsonial loading.

The moment of inertia for a given section from a long structure is calculated by the following formula. The formula measures a sectional area A. It's moments of inertia about the x-axis and y-axis passing through point O (in this study O is represented by the centre of gravity) are given by:

$$I_{xx} = \int y^2 \, dA$$

$$I_{yy} = \int x^2 \, dA$$

The distribution of *I* was calculated from the distal through to the proximal region of each plated tibia. The values obtained from the operated tibiae were compared with *I* values from the unoperated tibia. Cross-sectional area, the polar moment of the area *(Ip),* the moment of inertia of the area with respect to the transverse axis *(I_{xx})* and the sagittal axis *(I_{yy})* were measured using Cosmos/M software (version 1.71; Structural Research and Analysis Corporation) *(fig. 4)*. The titanium alloy used in this study was titanium 318 containing 4% aluminium and 6% vanadium and had an elastic modulus of 106 GPa, a Poisson's ratio of 0.33 and a density of 4.42×10^{-6} kg/m^3. The elastic modulus of bone was 20GPa, and the Poisson's ratio 0.36 (Kimura and Amtmann, 1984). The density of goat tibial cortical bone was calculated using the following formula:

$$\text{Density} = \frac{\text{Mass}}{\text{Volume}}$$

Three sections of different thickness were taken from a goat tibia. The change in volume when each was added to 1.0 ml of water was noted and density calculated. The results obtained were averaged and the value used in FE analysis was 1.937×10^{-6} kg/m^3. Thus, I assumed that the density and therefore elastic modulus of each of the goat tibiae were the same.

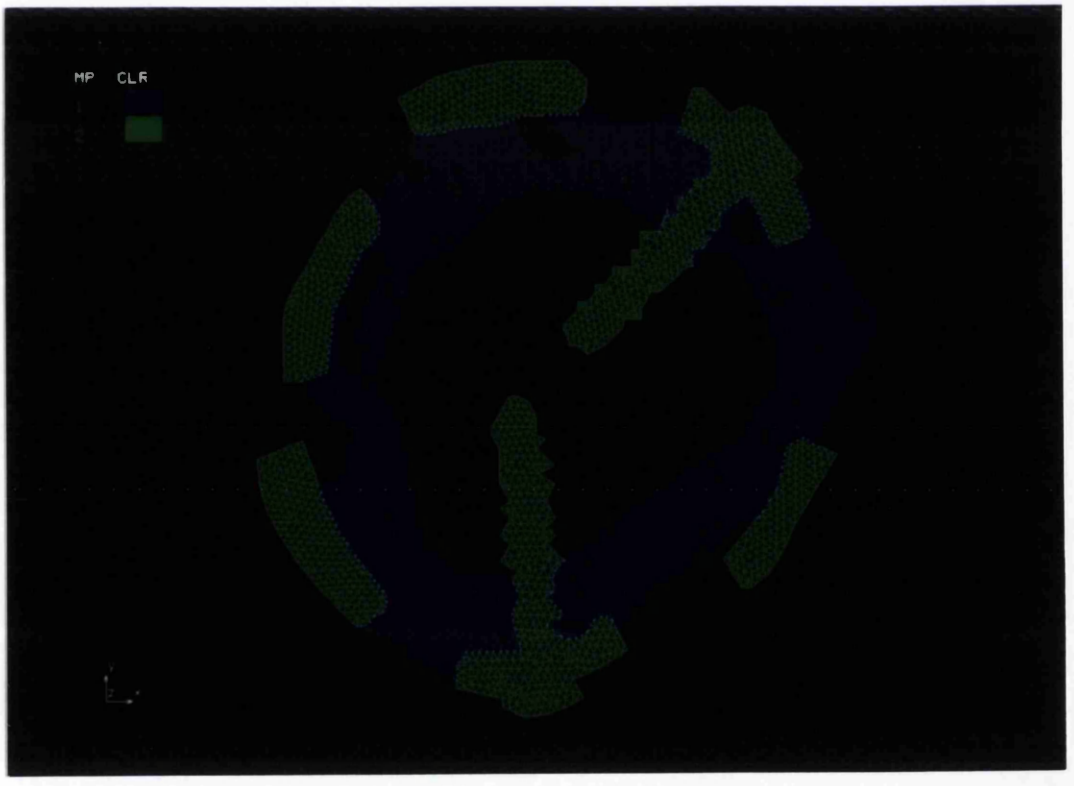


Figure 4: A photograph showing the mesh created using FEA software on a transverse section through the 6 plated implant design.

4.2.4 STATISTICS

Data was initially tested for normality (Statworks™ version 1.2; Cricket Software, 1985). P-values >0.05 were considered normal and values obtained following the normality test in this chapter were >0.05 and therefore the unpaired student's *t-test* was used where p-values less than 0.05 were classified as significant.

4.3 RESULTS

No wounds became infected and all goats remained healthy and maintained their weight throughout the 6 month post-operative period. The animals were able to stand and walk immediately after surgery but were non-weight bearing on their operated limbs. "Toe-touching" was observed after about a week. Six weeks post-operatively the goats appeared to have normal activities without limping and were able to stand on both hind limbs. The design of prostheses did not affect recovery from the operative procedure.

4.3.1 HISTOLOGICAL RESULTS

The initial biological and mechanical alterations caused by extra-cortical plate fixation resulted in the formation of woven bone observed 25 days post surgery. The woven bone formed an interconnected structural scaffold and occupied the area beneath the plates and at intermittent regions along the periosteal surface.

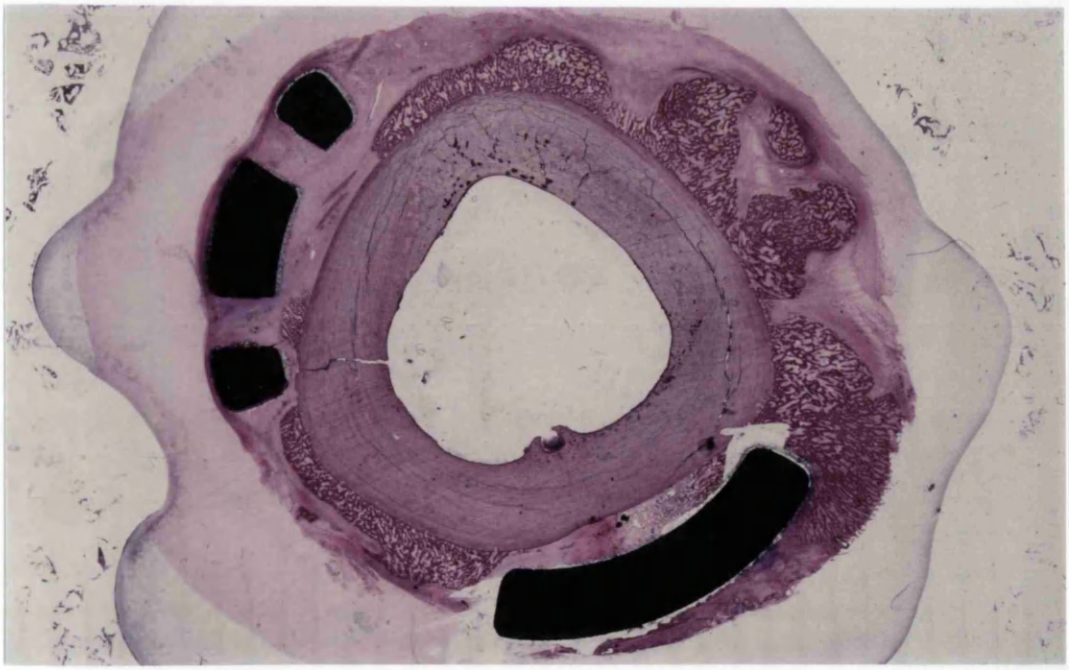


Figure 5: A photomicrograph showing woven bone on the periosteal surface 25 days post surgery (Mag x1).

An intermediate stage of bone maturation was observed at 2 months where woven bone was still identified but was being remodelled and gradually replaced by lamellar bone *(fig.6)*. At this stage bone had grown into the slots

and above the plates with widespread direct bone-implant integration. At 6 months woven bone around the extra-cortical plates had been replaced with lamellar bone and well organised Haversian systems *(fig.7)*. There was no discontinuity between the newly formed bone and the cortical bone.

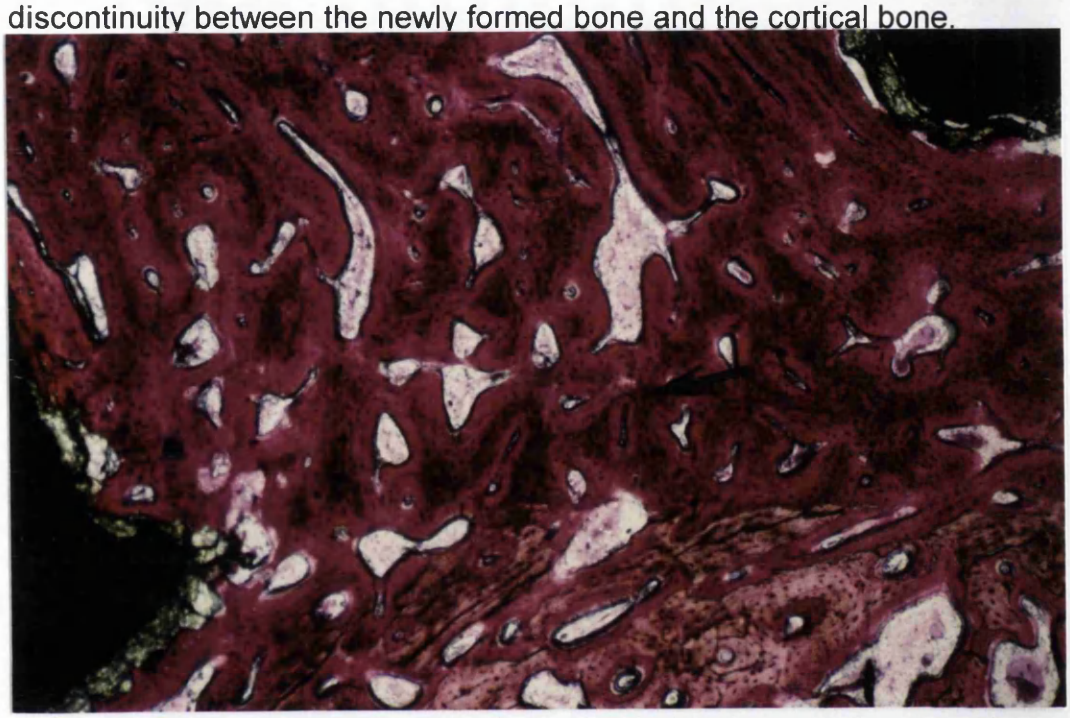


Figure 6: A photomicrograph demonstrating bone maturation where woven bone (arrowed) is being replaced by lamellar bone (Mag x4).

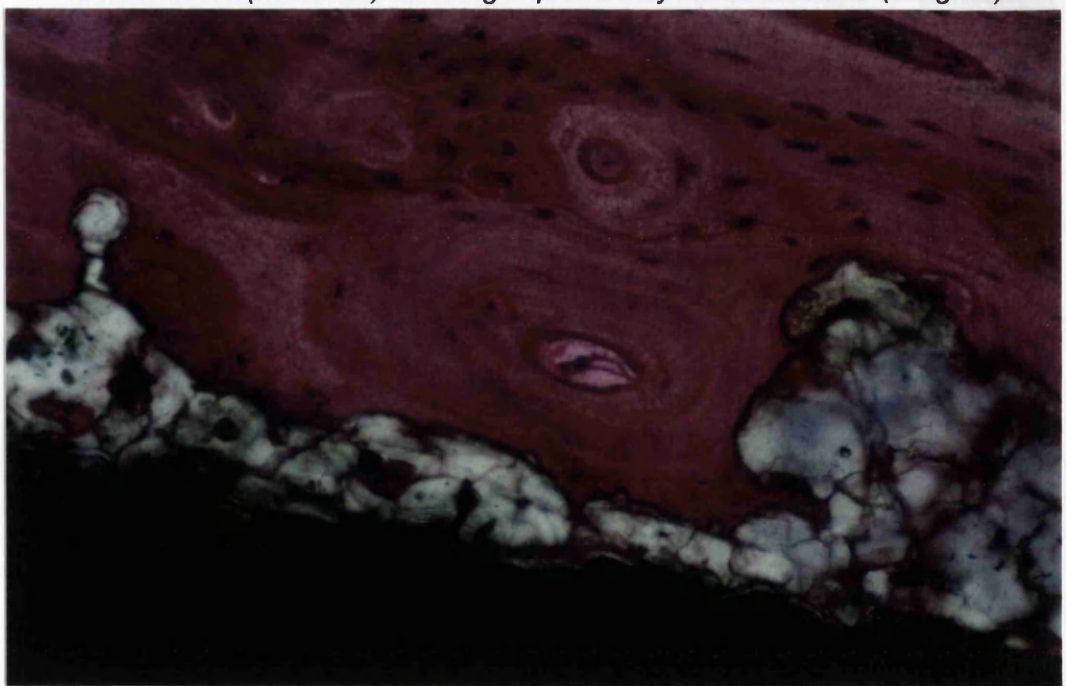


Fig 7: A photomicrograph of bone organised into haversian systems adjacent to the implant surface at 6 months post implantation (Mag x10).

In regions where bone-implant union did not occur a fibrous tissue interface was observed consisting of collagen fibrils and fibroblasts orientated parallel to the interface. Discrete areas of hydroxyapatite fragmentation resulted in the formation of hydroxyapatite particles of varying sizes. Small particles (~5μm) of hydroxyapatite prompted localised macrophage and foreign-body giant cell infiltration. Larger fragments of HA (~10μm) were completely engulfed by bone and appeared to be well tolerated. In areas where the HA coating had delaminated, bone was observed between the coating and in direct contact with the exposed titanium alloy surface.

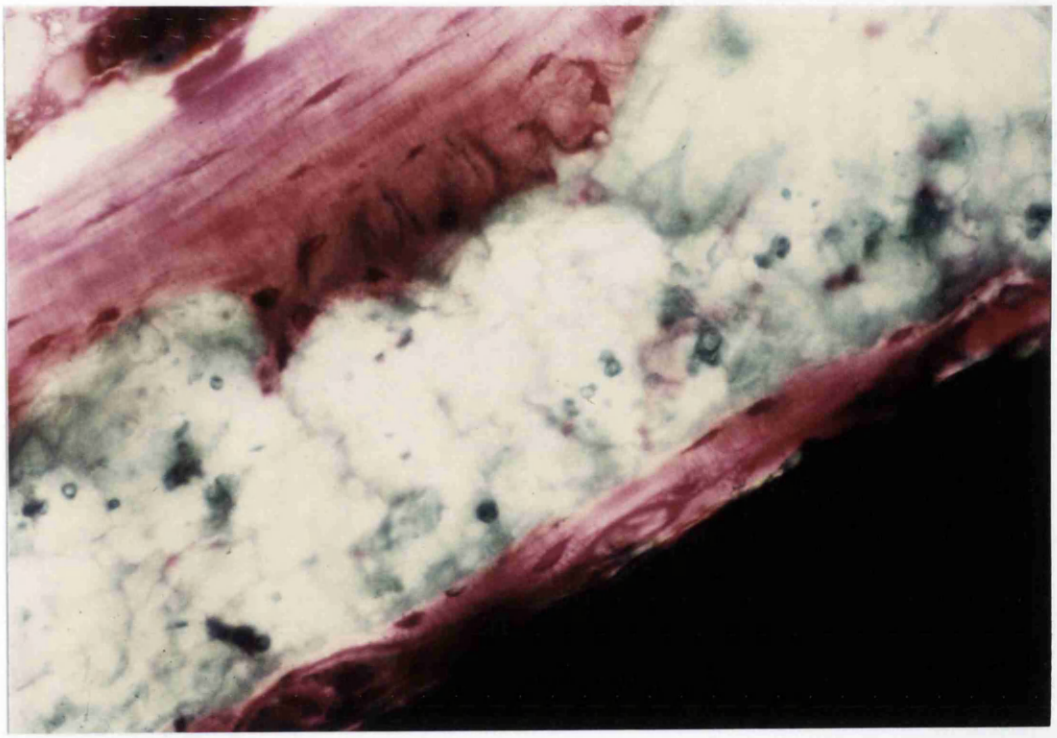


Figure 8. A photomicrograph showing delamination of the HA coating from the titanium surface. Bone is seen growing between the coating and implant surface (Mag x10).

Radiographs taken of the retrieved tibiae showed that in all but one case an uninterrupted bridge of bone had formed over the entire length of the prosthetic shaft joining the segmented tibiae together *(fig.9)*. Bony ingrowth had occurred into the HA coated and grooved collar and around the HA coated extra-cortical plates.

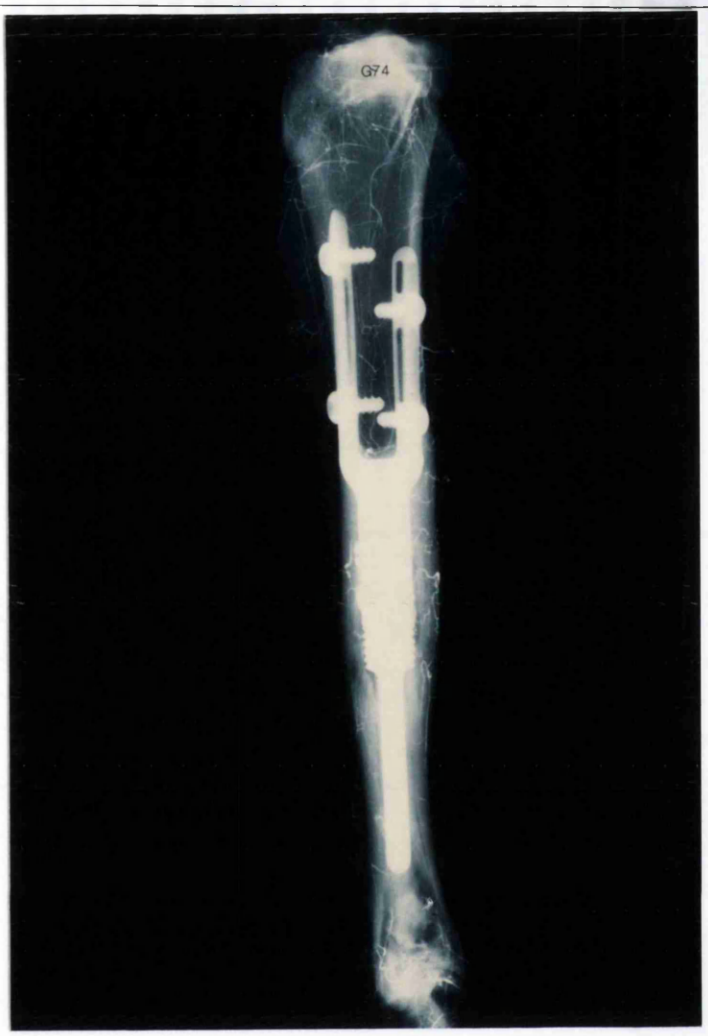


Figure 9: A radiograph of a retrieved tibia 6 months after surgery. Bone has grown over the shaft of the implant uniting the proximal and distal segments of bone.

Contact radiographs of serial slices taken through the tibiae showed that a combination of bone formation and bone resorption had occurred in response to extra-cortical plate fixation. All of the plate designs in this study induced disorganised cortical activity. The degree of bony adaptation and induced cortical porosis depended on the implant design and on the position of the section along the tibia. Figure 10 is a two-plated implant design retrieved 6 months after surgery. Figures 10a, 10b and 10c are transverse sections through the proximal, mid and distal regions of this plated tibia respectively. For comparison, figure 11 is photograph of the six-plated implant design. Figures 11a, 11b and 11c are all transverse sections

through the same 6 plated implant in the proximal, mid and distal regions respectively.

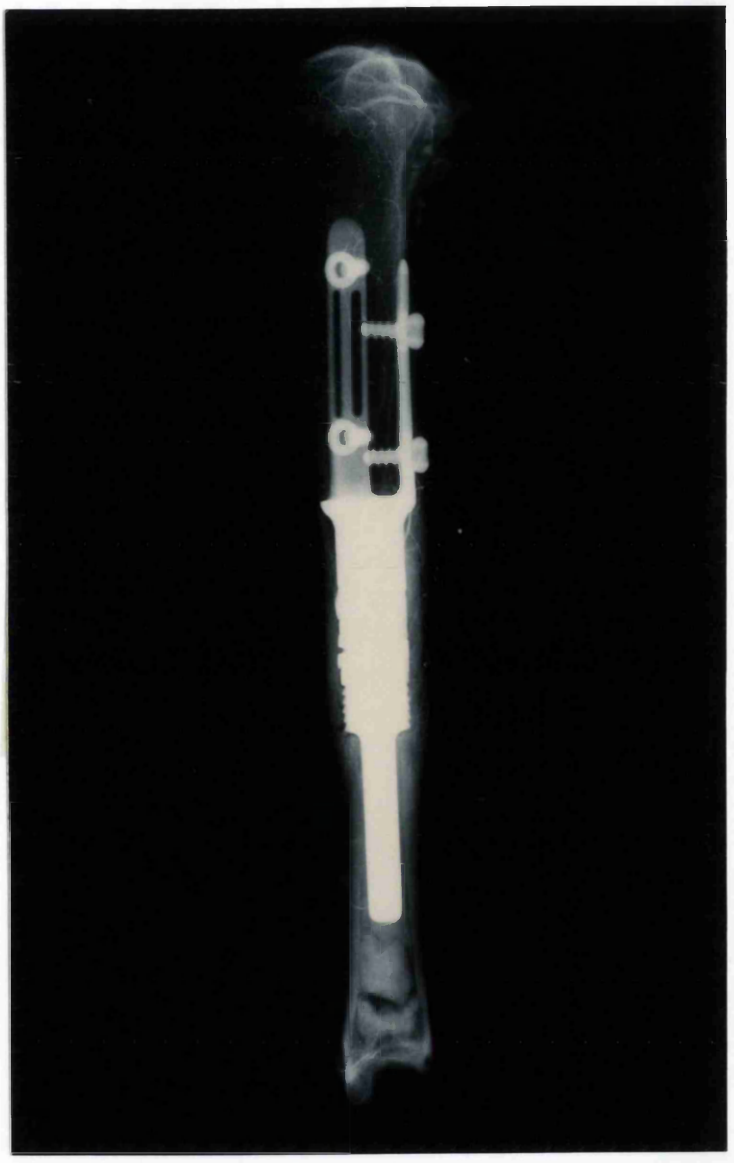


Figure 10: A radiograph of a two plated prosthesis retrieved 6 months after surgery.

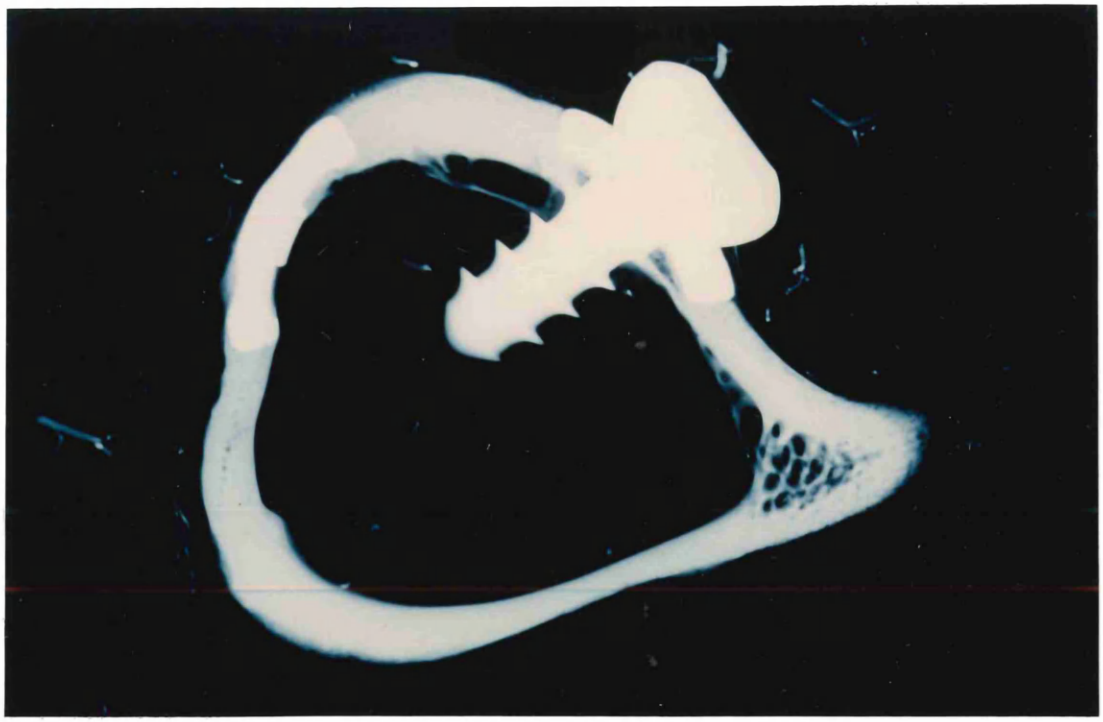


Figure 10a. A radiograph of a transverse section through the proximal region of the 2 plated implant shown in fig. 10.

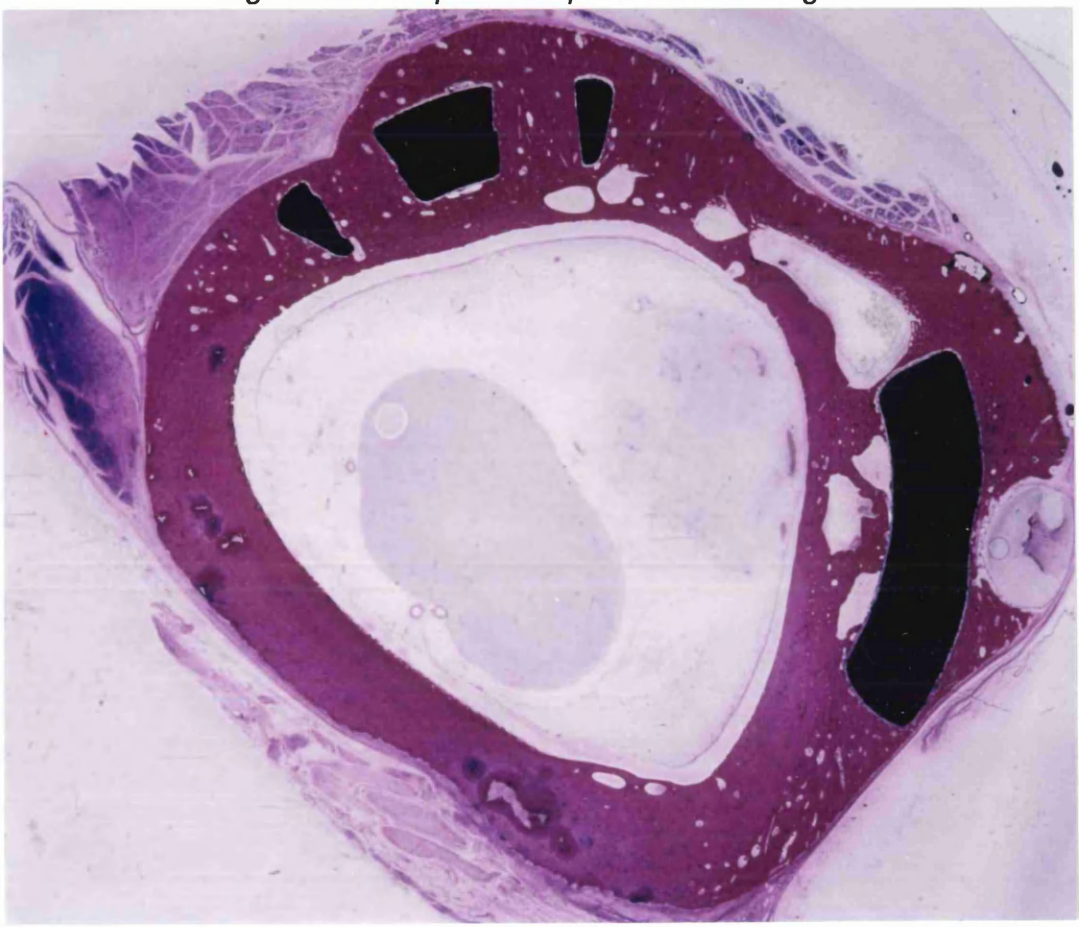


Figure 10b: A transverse histological section through the mid region of the 2 plated implant shown in fig. 10.

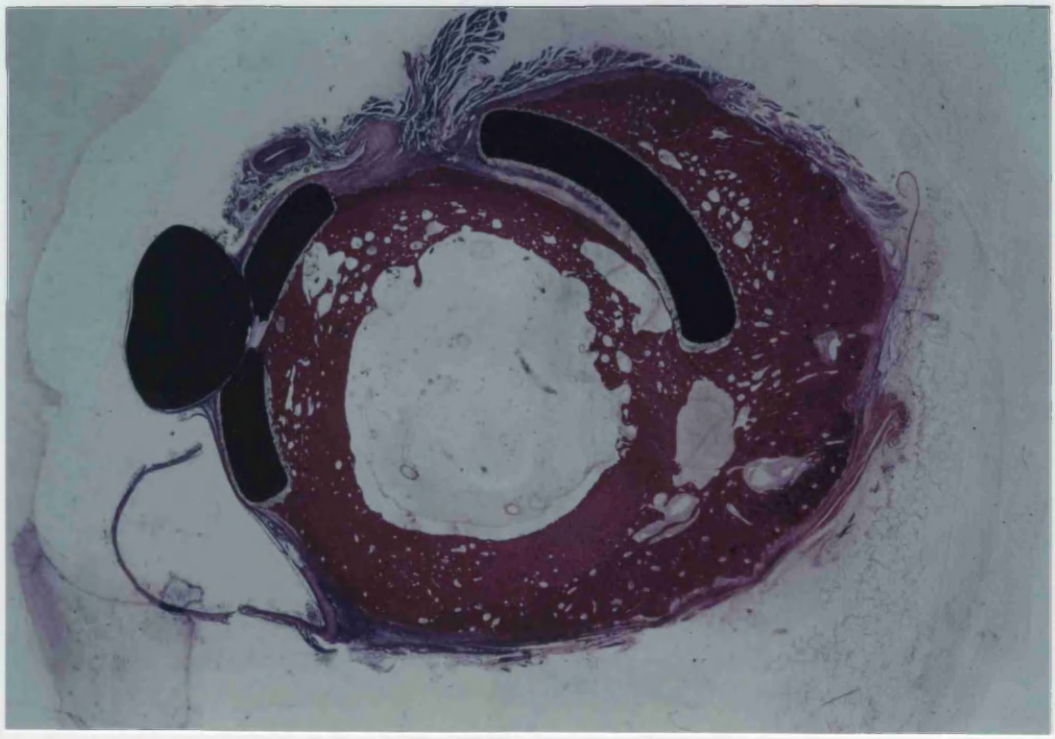


Figure 10c: A transverse histological section through the distal region of the implant shown in fig. 10.

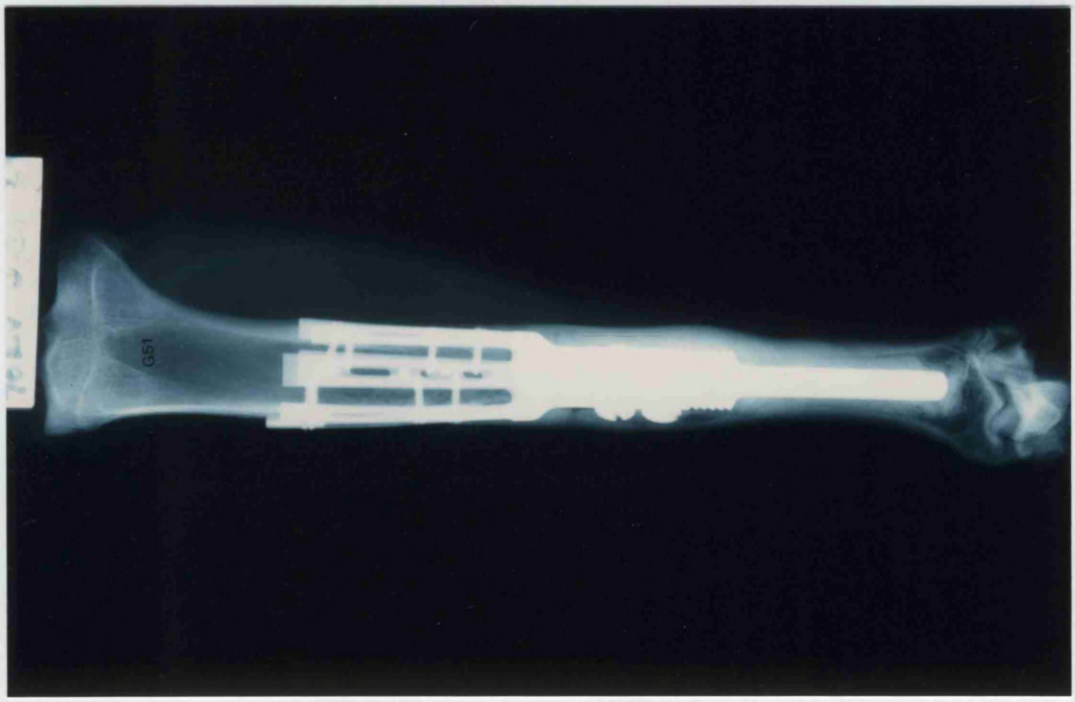


Figure 11: A photoradiograph of the six plated implant design.

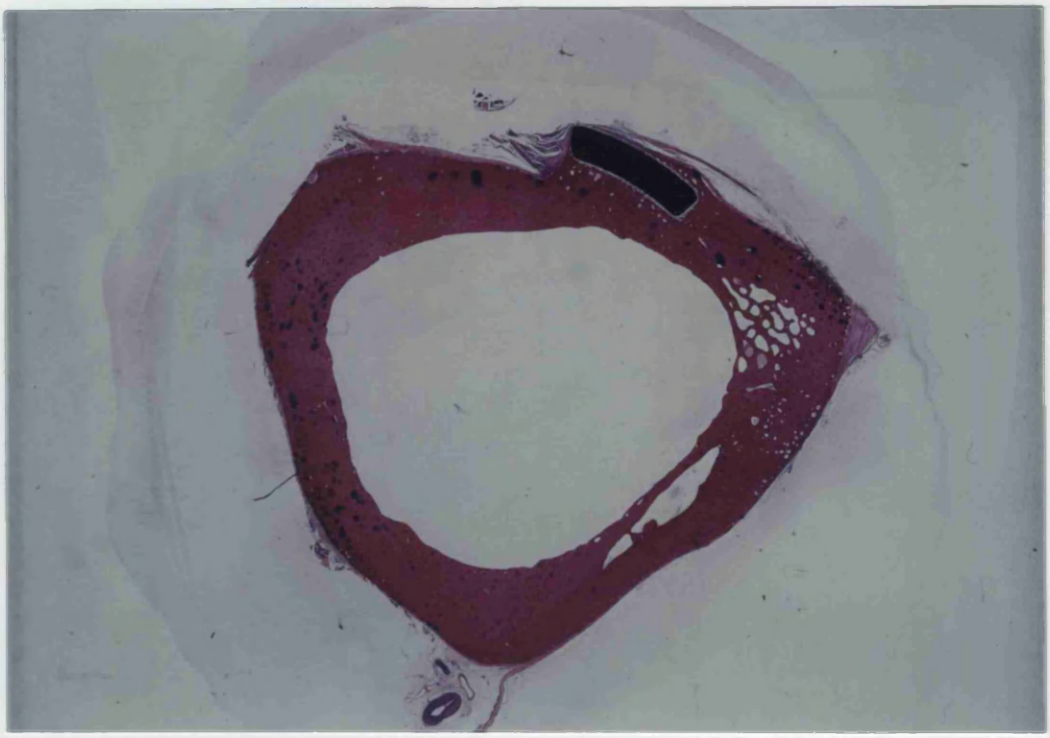


Figure 11a: A transverse histological section through the proximal region of a 6 plated implant.

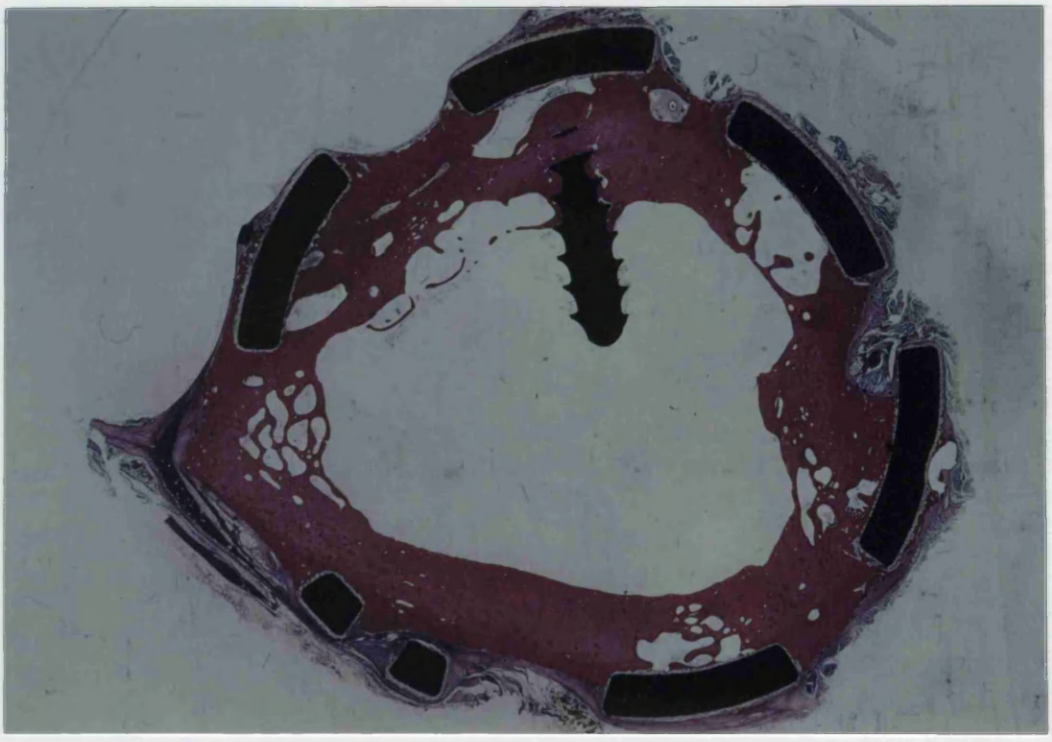


Figure 11b: A transverse histological section through the mid region of the 6 plated implant.

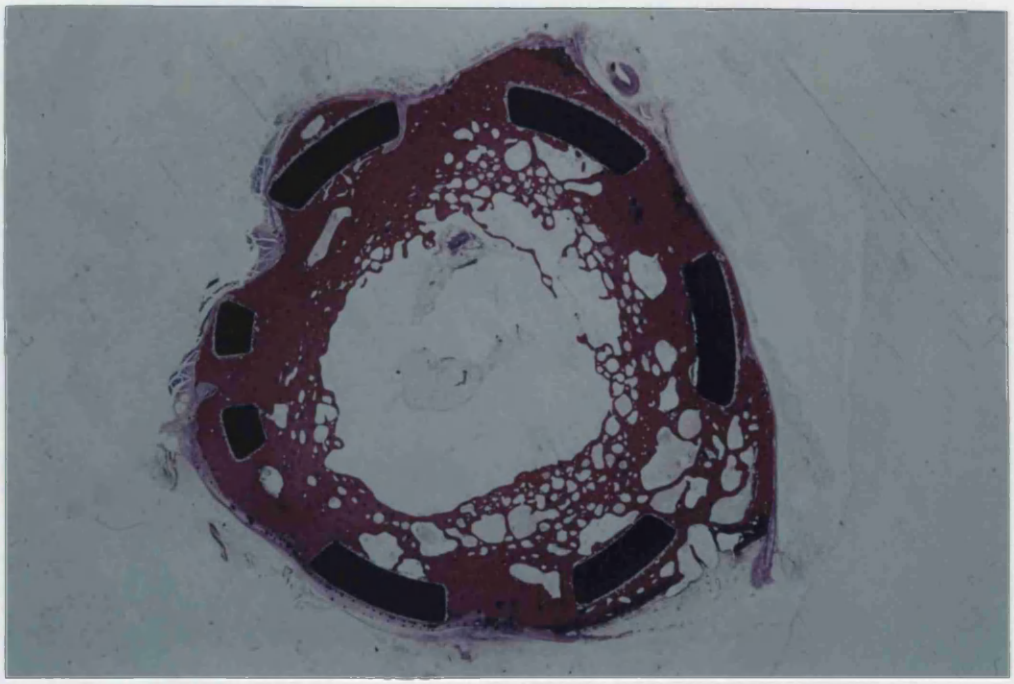


Figure 11c: A transverse histological section through the distal region of the 6 plated implant.

In all cases, most cortical porosis was seen distally next to the transection site. Sections taken through the proximal regions usually demonstrated plates that were well integrated into a dense tibial cortex. In all cases bone apposition onto the external surface of the plate occurred through a combination of periosteal bone formation, invasion of bone through slots and bone growth over the ends of the plate.

Porosis was most pronounced in the cortex under the stiffer unslotted plate designs. Qualitative observations revealed less cortical porosis beneath the slotted and more flexible plates. This was sometimes seen in the same cross-sectional area of bone *(fig.12)*.

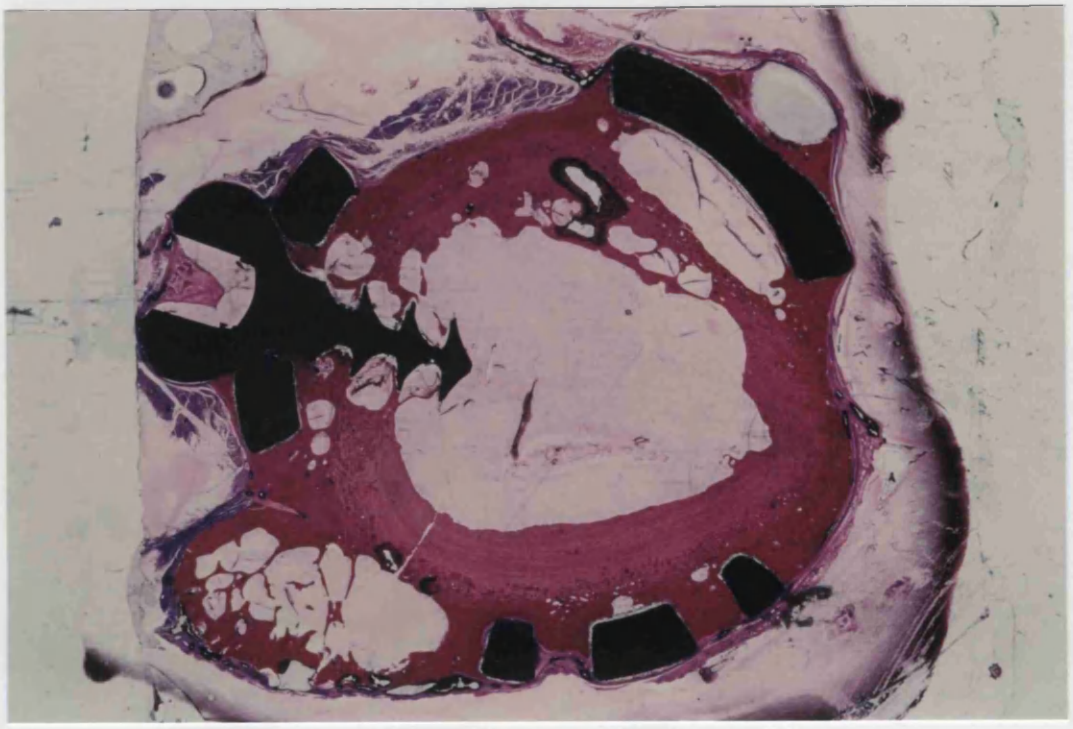


Figure 12: A transverse histological section through a three-plated implant showing bone ingrowth into the slots of a plate and a region of porosis beneath an unslotted plate.

4.3.2 TETRACYCLINE BONE MARKING RESULTS.

Results obtained from fluorescein markers in bone adjacent to the extra-cortical plates showed greater bone formation rates when compared with the unoperated bone. Cement lines and osteoid were evident separating the newer areas of bone *(fig. 13)*. The markers were incorporated into remodelling Haversian systems in a regular concentric, centrifugal manner *(fig. 14)*. The tetracycline markers were incorporated in a more linear fashion in areas adjacent to the plates. Bone located around the edges of the plates was also intensely labelled *(fig. 15)*.

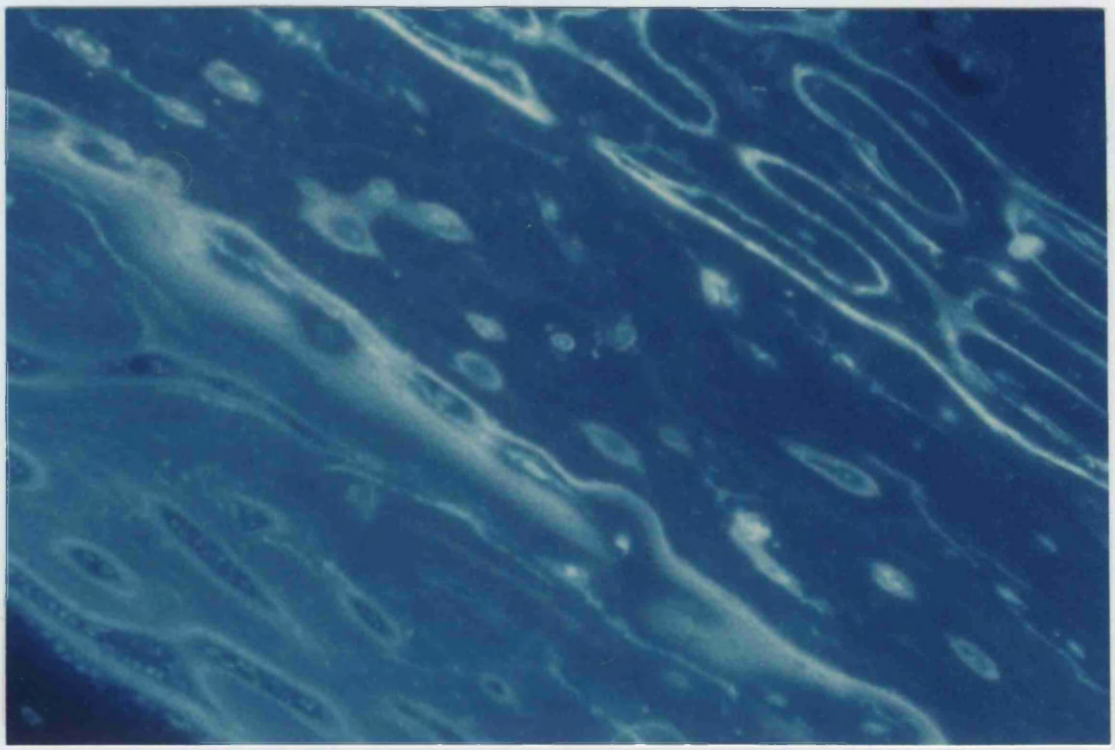


Figure 13: A thin section viewed under UV light demonstrating the osteoid seam (white), oxytetracycline (yellow) and demethylchlorotetracycline (orange) uptake by bone (Mag x10).

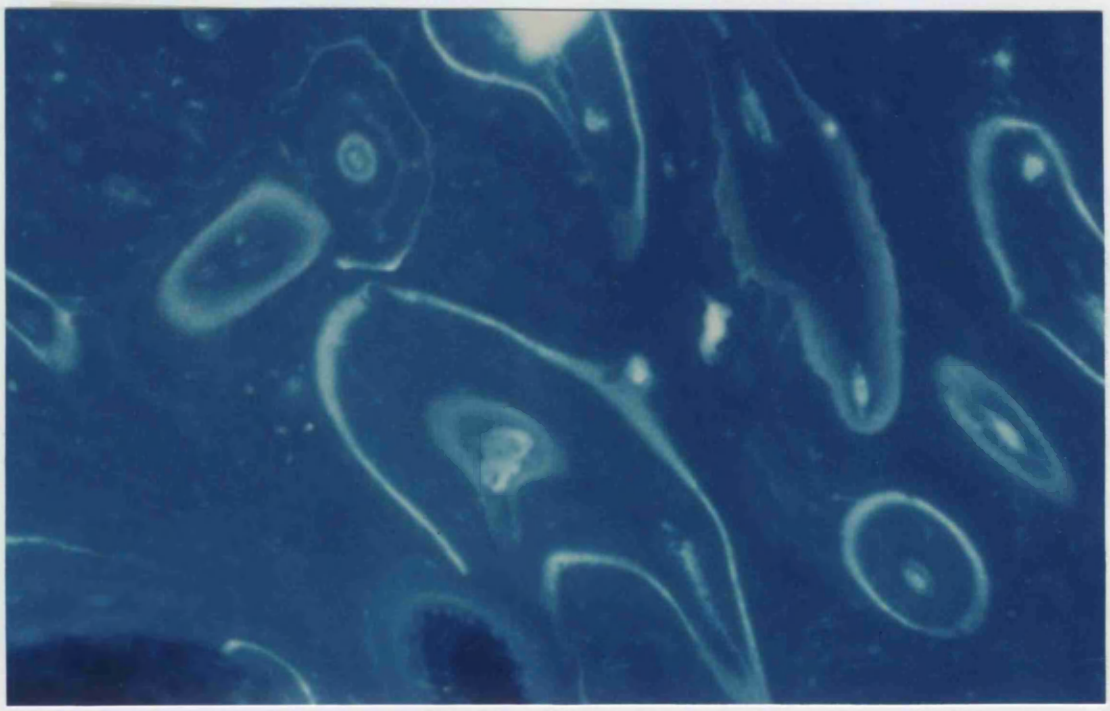


Figure 14: A thin section viewed under UV light showing tetracycline incorporation into remodelling haversian systems in a regular, concentric, centripetal manner (Mag x10).

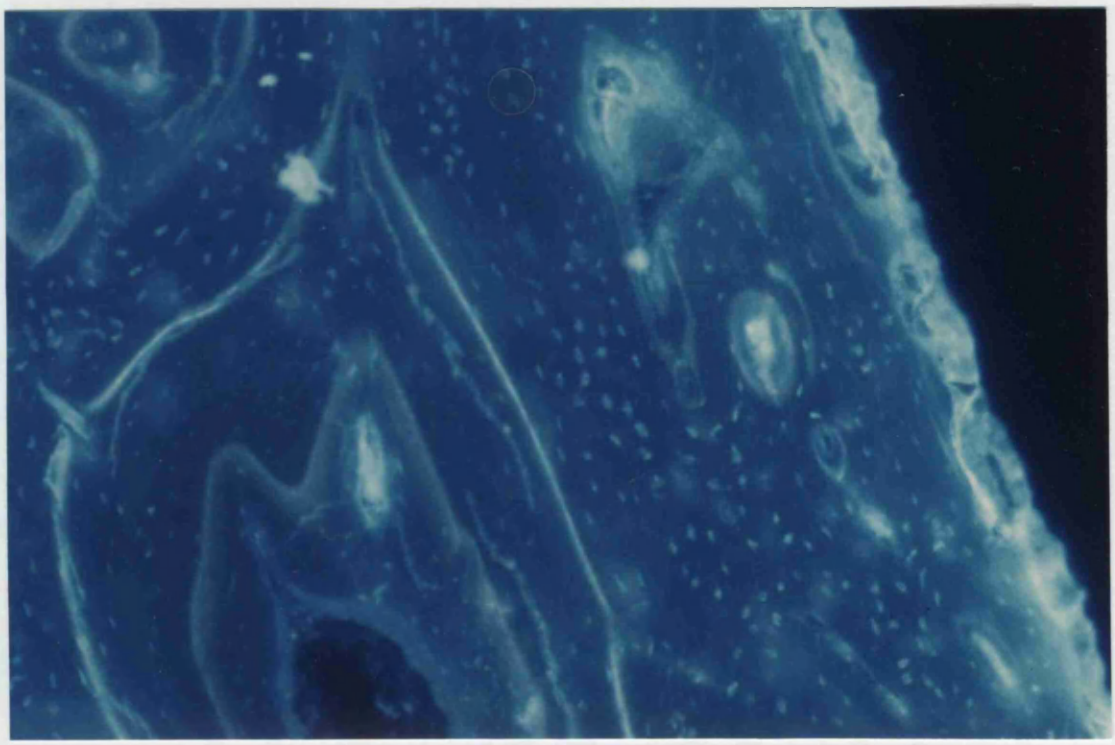


Figure 15: A thin section viewed under UV light adjacent to the extra-cortical plate. Bone is seen to remodel in a linear fashion over the surface of the plates (Mag x10).

The bone formation rate was calculated in μm day^{-1} and values were compared to unoperated cortical bone turnover (0.8211 μm day^{-1}). The highest growth rate was observed as bone grew into the slots of the plates (6.45 μm day^{-1}) *(Table 1, fig. 16)*. Significantly more bone formation occurred as bone grew into a slot when compared with normal cortical bone turnover ($p=<0.05$). The turnover rate increased as bone grew over slotted extra-cortical plates but significantly decreased when bone was measured in the same regions growing over the unslotted plate ($p=0.003$). Likewise, significantly higher rates of bone turnover were measured in bone beneath slotted plates when compared with regions below the unslotted plates ($p=<0.05$). P-values obtained are presented in Table 2.

Table 1. Bone turnover rates: a comparison of regions around plates.

	AVERAGE μm day^{-1}	Standard Error
Cortical Bone	0.8211	0.1433
Bone in slot	6.45	0.6779
Under slotted plate	4.3925	0.5876
Above slotted plate	2.404	0.2316
Under unslotted plate	1.0149	0.1696
Above unslotted plate	1.3695	0.1881

Table 2. P-value comparison of regions around plates.

	Cortical bone	Bone in slot	Under slotted plate	Above slotted plate	Under unslotted plate	Above unslotted plate
Cortical bone						
Bone in slot	<0.05					
Under slotted plate	<0.05	0.029				
Above slotted plate	<0.05	<0.05	0.001			
Under unslotted plate	0.411	<0.05	<0.05	0.001		
Above unslotted plate	0.053	<0.05	<0.05	0.003	0.191	

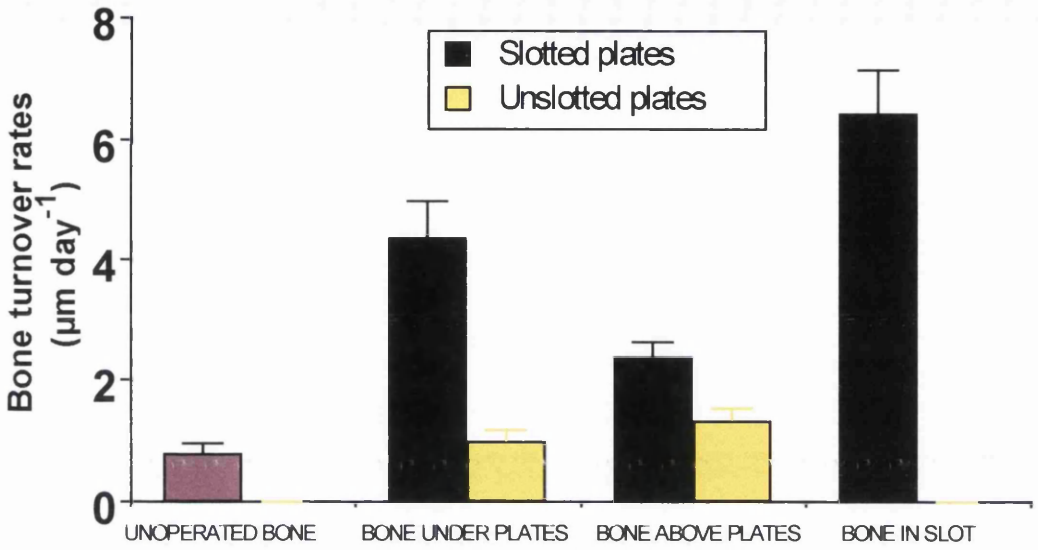


Figure 16: A graph comparing bone turnover rates in the various regions around slotted and unslotted plates (all designs).

4.3.3 IMAGE ANALYSIS OF TOTAL BONE AREA AND CORTICAL POROSITY.

Total bone area was measured using image analysis from serial transverse slices through each tibia. Sections obtained from the unoperated tibiae were averaged, results showed how bone area increased in the distal to proximal direction along the tibia *(fig. 17)*. Results obtained from the operated tibiae were compared in the distal, mid and proximal regions. Results revealed no significant differences in bone area when all of the operated tibiae were grouped and compared with the unoperated tibia at the same level (distal p=0.611; mid p=0.513; proximal p=0.513) *(fig. 18)*.

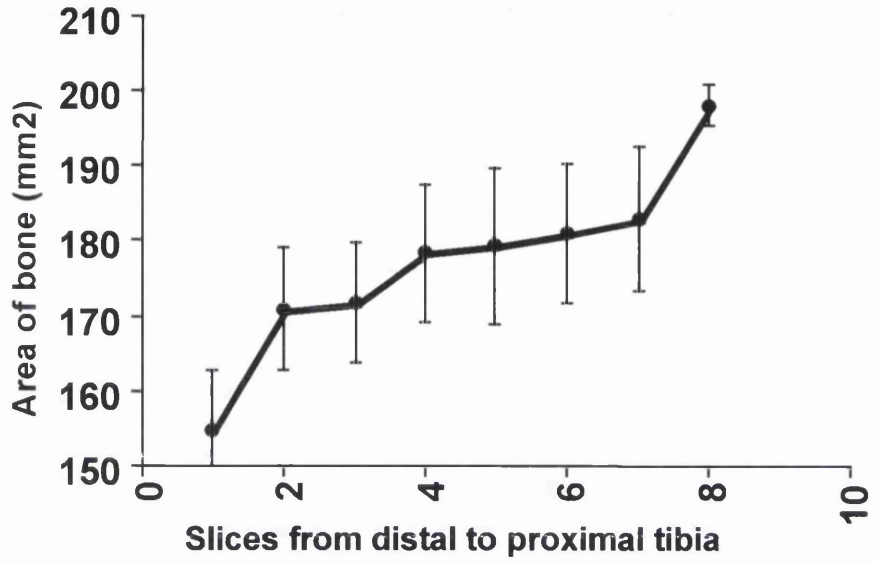
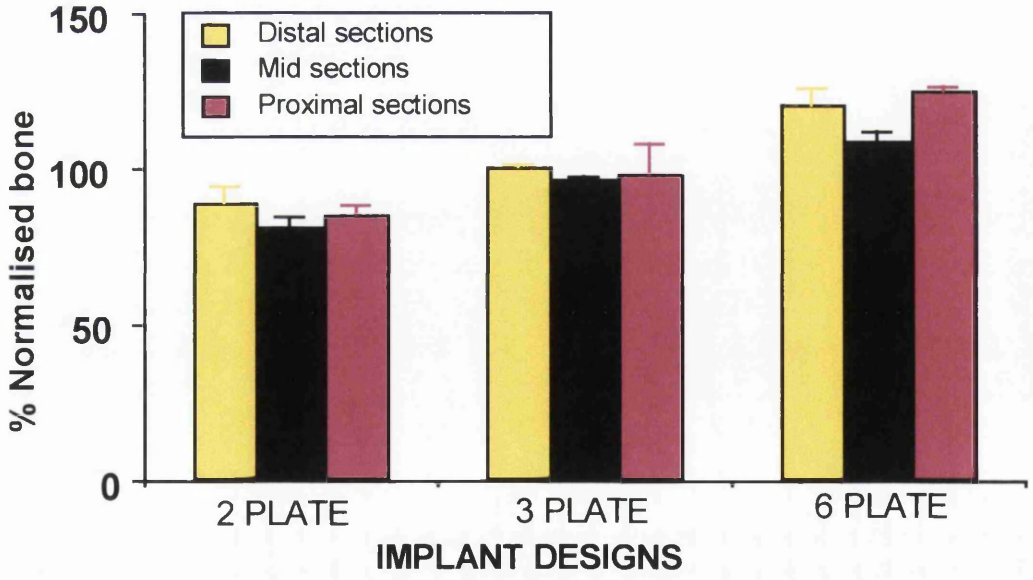


Figure 17: A graph demonstrating the distribution of total bone area averaged from all left unoperated tibiae.



* Values normalised against slices from unoperated tibiae (100%) taken at the same level

Figure 18: A graph demonstrating total bone area around the 3 implant designs.

When total bone area around the three different implant designs were compared it was found that significantly more bone surrounded the 6 plate design when compared with the 2 plate design (p= <0.05) and the 3 plate design (p= <0.05). Significantly more bone surrounded the 3 plate design when compared with the 2 plate design (p=<0.05). However, there appeared to be no correlation between the cross-sectional area of implant present in each section and an increase in bone formation as demonstrated in the graph below *(fig. 19)*.

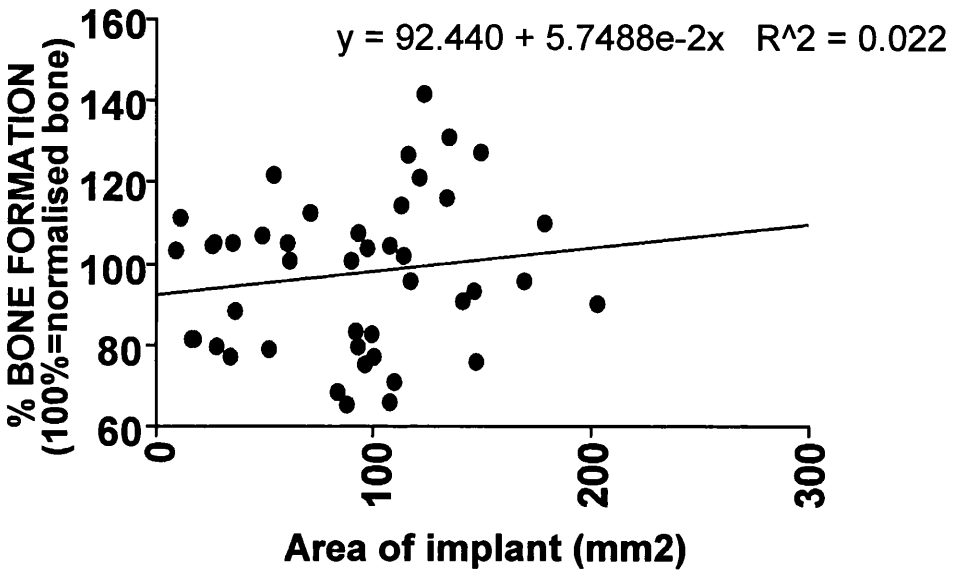


Figure 19: A graph demonstrating the relationship between cross sectional area of implant present and %bone formation.

No significant difference was found when total bone area around the 3 plated design was compared with the contralateral tibia (p=0.63). However, significantly more bone was present around the 6-plated implant when compared with the contralateral tibia (p= 0.002). In contrast, even though bone remodelling did occur with bone formation around the plates, there was significantly less bone overall adjacent to the 2-plated design when compared with the left tibia (p=0.001).

Image analysis techniques also measured cortical porosity in each cross sectional area of tibia. Results demonstrated that when all slices were grouped together, most cortical porosis occurred in bone beneath the 6 extra-cortical plate implant design. Less porosis was seen in bone beneath the 3 plated design although this value was not significant (p=0.068). Significantly less porosis was measured in bone beneath the 2 plated implant design when compared with both the 6 plate design ($p<0.05$) and the 3 plated implant design (p=0.004) *(fig. 20)*.

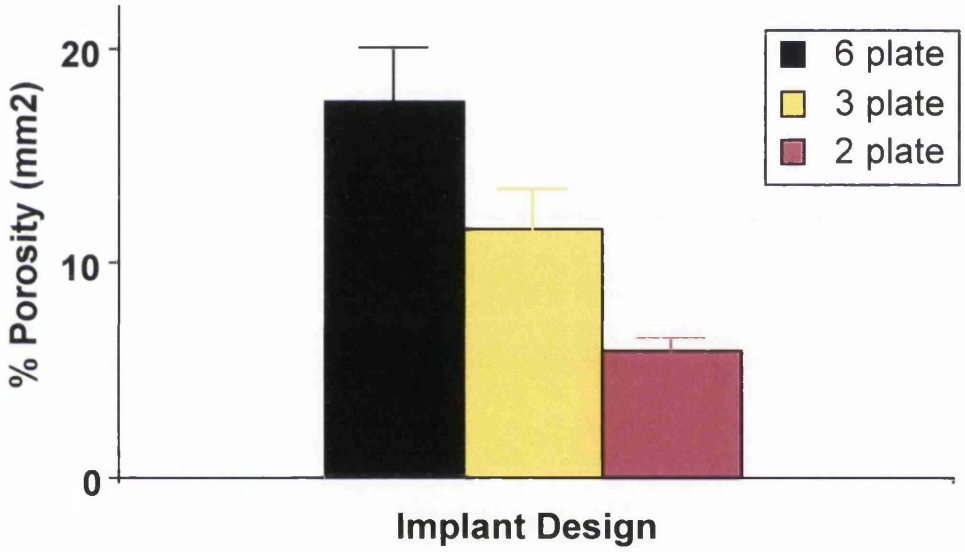


Figure 20: A graph comparing % bone porosity in the 2, 3 and 6 plated implant designs.

Cortical porostiy was also compared in the proximal, mid and distal regions of each implant design. Results demonstrated a general trend where most porosis was observed in the distal region and least in bone beneath the proximal region of the plates *(fig. 21)*. Table 3 shows the mean and standard error values obtained for porosity in the proximal, mid and distal regions of the three implant designs. Tables 4a,b,c present p-values obtained when the three implant designs are compared in these regions. Tables 5a,b,c compares %porosity in proximal, mid and distal regions within each design.

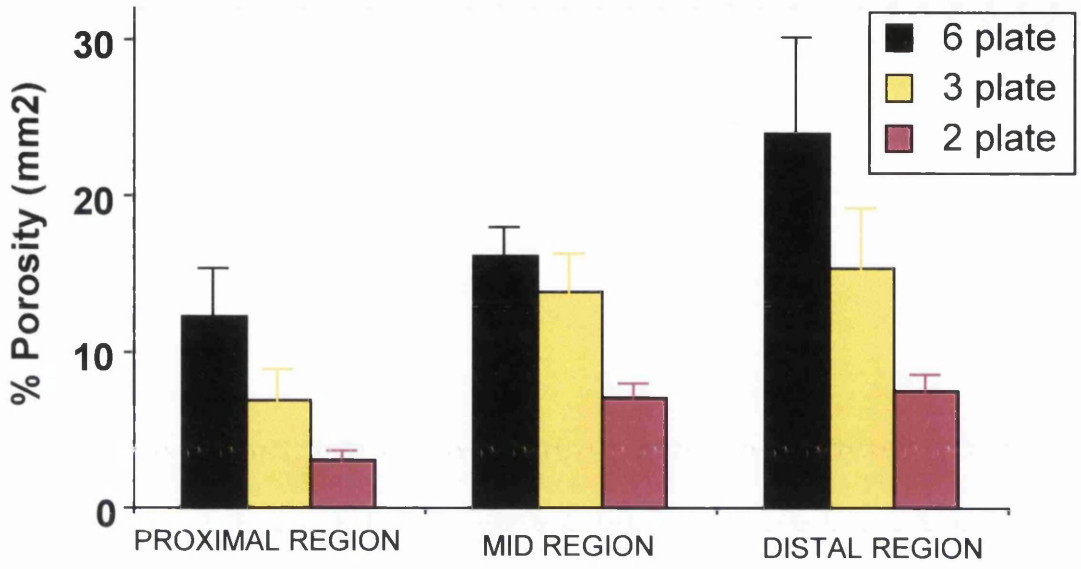


Figure 21: A graph comparing % porosity in the proximal, mid and distal regions of all three implant designs.

Table 3. % Cortical porosity: results in the proximal, mid and distal regions of the three implant designs.

		Mean %porosity(mm2)	Standard Error
	Prox.	12.318	3.069
6 plate design	Mid.	16.215	1.787
	Dist.	24.066	6.153
	Prox.	6.849	2.136
3 plate design	Mid.	13.789	2.472
	Dist.	15.309	3.998
	Prox.	3.15	0.538
2 plate design	Mid.	7.141	0.911
	Dist.	7.549	1.006

Table 4a. A p-value comparison of %porosity in the **proximal** region of three implant designs.

	6 plate design	3 plate design	2 plate design
6 plate design			
3 plate design	0.168		
2 plate design	0.007	0.124	

Table 4b. A p-value comparison of %porosity in the **mid** region of the three implant designs.

	6 plate design	3 plate design	2 plate design
6 plate design			
3 plate design	0.475		
2 plate design	0.001	0.024	

Table 4c. A p-value comparison of %porosity in the **distal** region of the three implant designs.

	6 plate design	3 plate design	2 plate design
6 plate design			
3 plate design	0.254		
2 plate design	0.011	0.07	

Table 5a. A p-value comparison of %porosity in the 6 plate implant design.

6 plate design	Prox.	Mid.	Dist.
Prox.			
Mid.	0.315		
Dist.	0.138	0.266	

Table 5b. A p-value comparison of %porosity in the 3 plate implant design.

3 plate design	Prox.	Mid.	Dist.
Prox.			
Mid.	0.061		
Dist.	0.081	0.755	

Table 5c. A p-value comparison of %porosity in the 2 plate implant design.

2 plate design	Prox.	Mid.	Dist.
Prox.			
Mid.	0.004		
Dist.	0.003	0.77	

4.3.4 ANALYSIS OF RIGIDITY OF IMPLANTS AND CORRELATION WITH BONE FORMATION

Figure 22 shows the second moment of area along the unoperated tibiae and compares the progression of second moment of area in A/P and M/L planes.

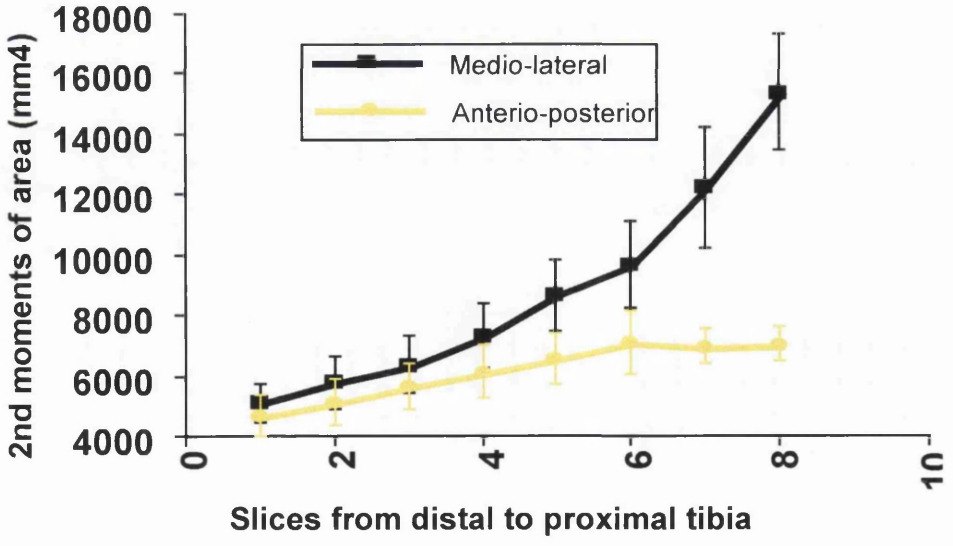


Figure 22: A graph demonstrating the second moment of area along the unoperated tibia.

Figure 23a compares the second moment of area in the AP plane (ML plane *fig. 23b*) of the three implant designs. The flexural rigidity of the bone was compared with average values from the unoperated left tibiae. The results presented in the following graphs represent the bending moments of the bone only. The effect of the metal implants has been removed.

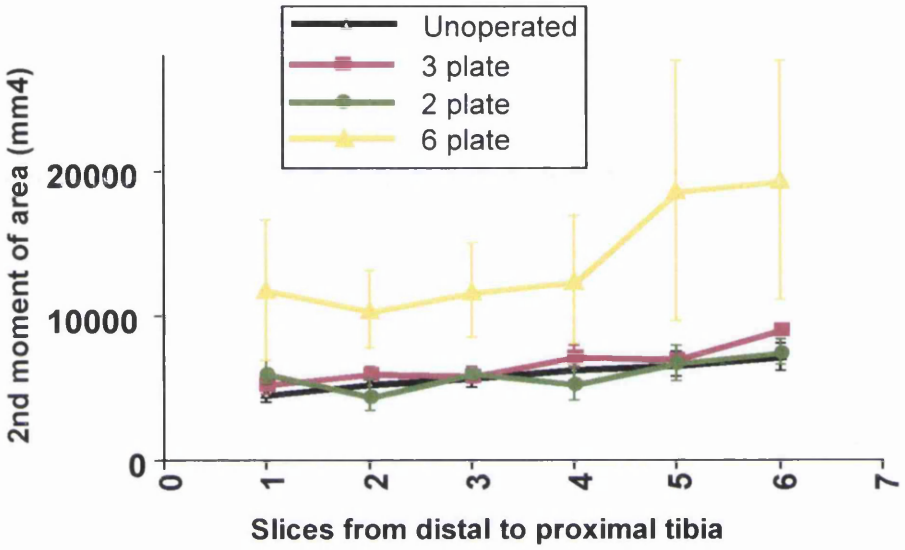


Figure 23a Second moment of area: a comparison of the three implant designs in the AP plane (effect of implant not included).

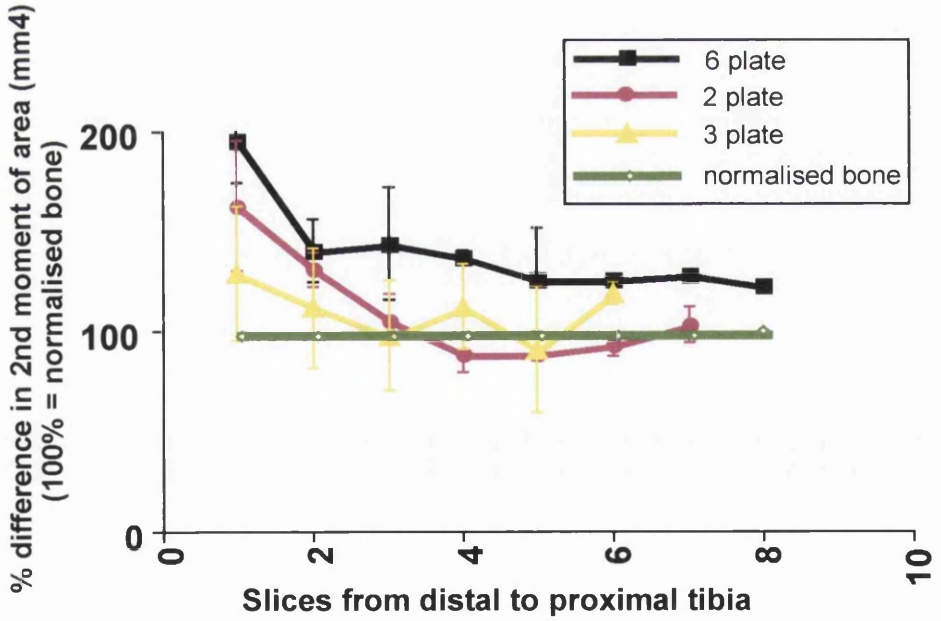


Figure 23b: Second moment of area: a comparison of the 3 implant designs in the ML plane (effect of implant not included).

Figure 24a compares the flexural rigidity of the bone when the implant contribution was included, in the AP plane and ML plane (*fig. 24b*). Thus, the second moment of area of the tibiae following extra-cortical plate attachment were compared with average values obtained from the unoperated contralateral tibiae. The graphs demonstrate that all implant designs increased the *I* of the tibia. The 6 plate and 3 plate designs significantly increased the second moment of area when compared with the left tibia (p=0.003 and 0.066 respectively). However, the 2 plate design did not significantly increase the second moment of area when compared with the left tibia (p=0.235).

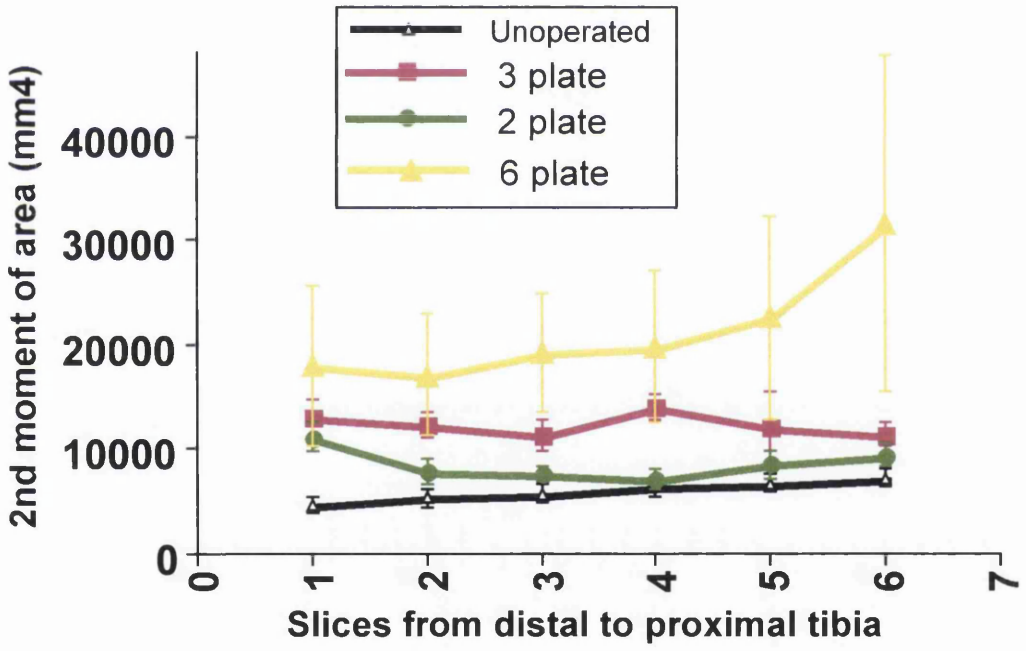


Figure 24a: Second moment of area: a comparison of 3 implant designs in AP plane (effects of implant included).

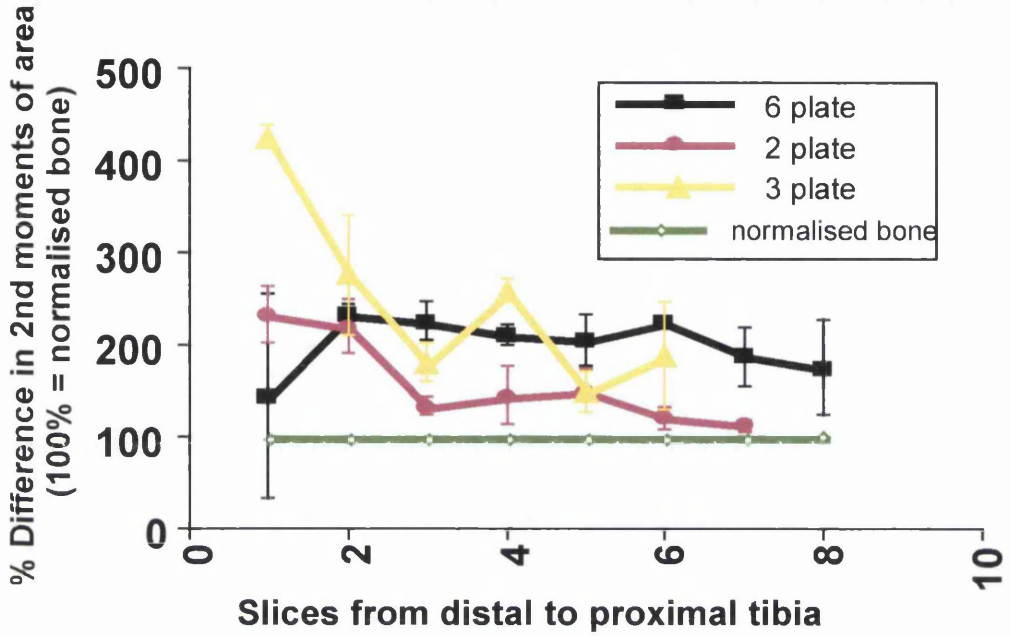


Figure 24b: Second moment of area: a comparison of 3 implant designs in the ML aspect (effects of implant included).

Results demonstrated that the 6 extra-cortical plate design was more rigid when compared with the 2 and 3 plate designs *(fig. 25a,b)*.

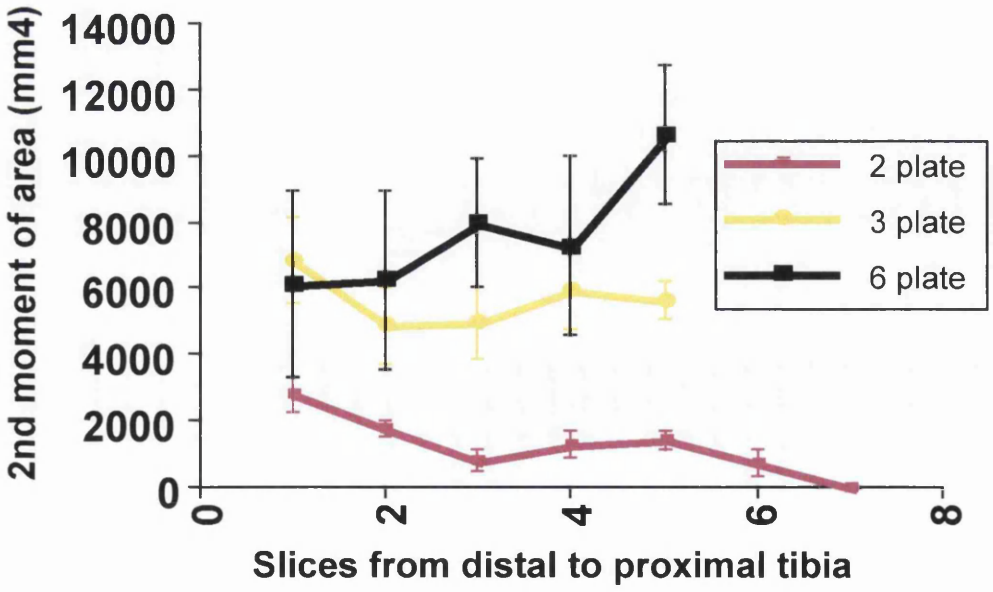


Figure 25a: A graph demonstrating second moment of area in the AP aspect.

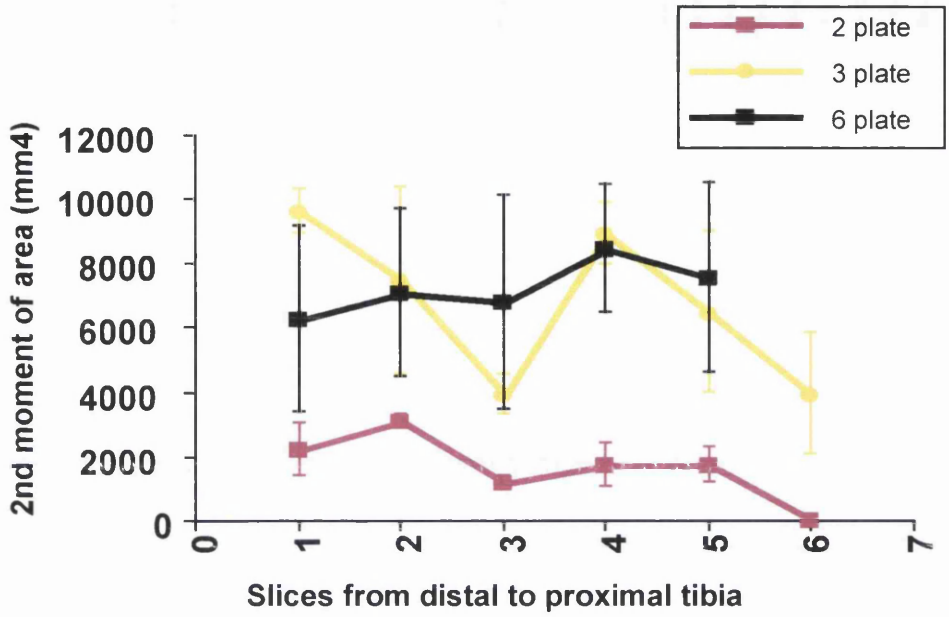


Figure 25b: A graph demonstrating second moment of area in the ML aspect.

Figures 26a and b demonstrated how the flexibility of the plates were related to the area (mm^2) of titanium present in each cross sectional slice of tibia (R2 =0.739 M/L; R2 =0.579 A/P).

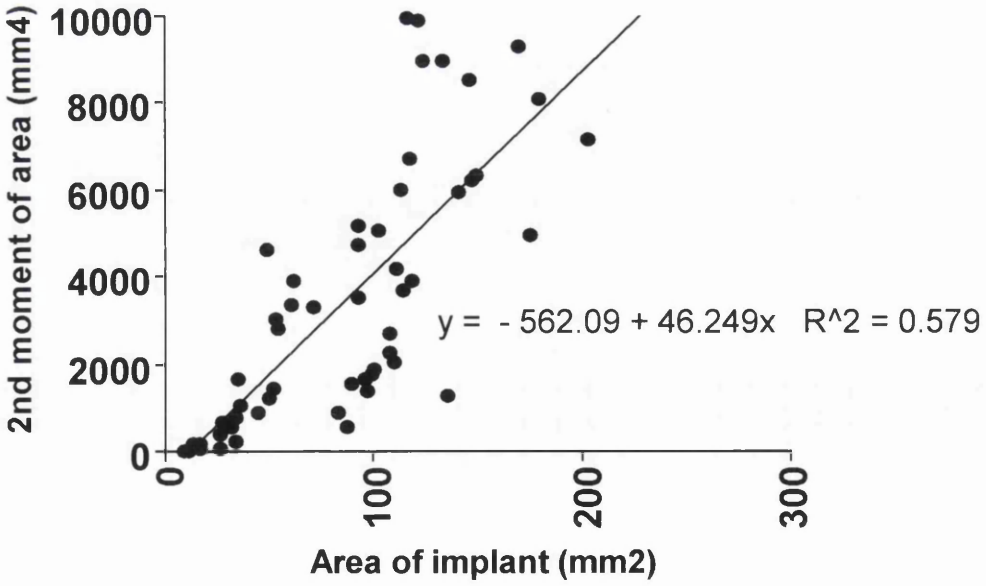


Figure 26a: A graph showing the correlation between cross sectional area of implant and I in the AP aspect.

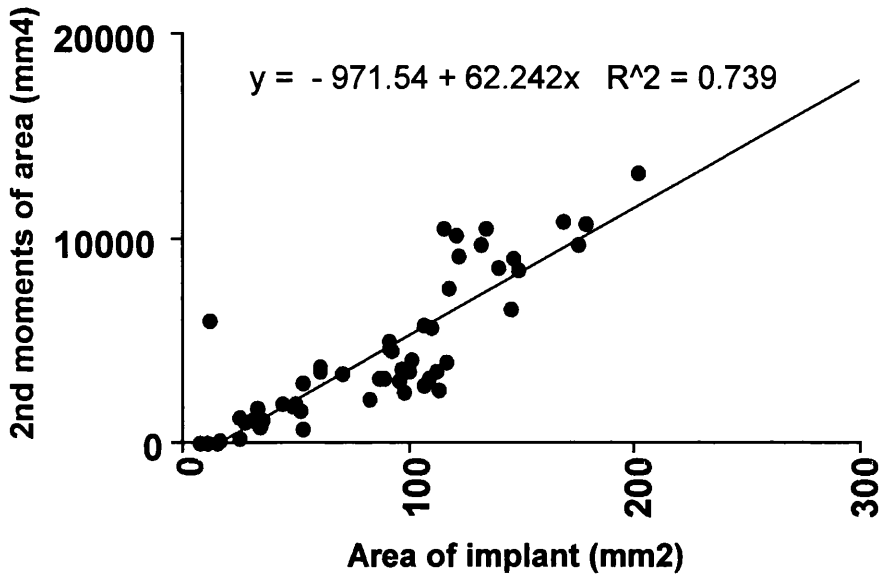


Figure 26b: A graph showing the correlation between area of implant and I in the ML aspect.

Results have shown that the 6 plated implant design was stiffest and induced most bone formation. However, there was no correlation between the second moment of area of the implant and increased bone formation in the AP (R2=0.283) *(fig. 27a)* or ML (R2=0.134) *(fig. 27b)* aspects.

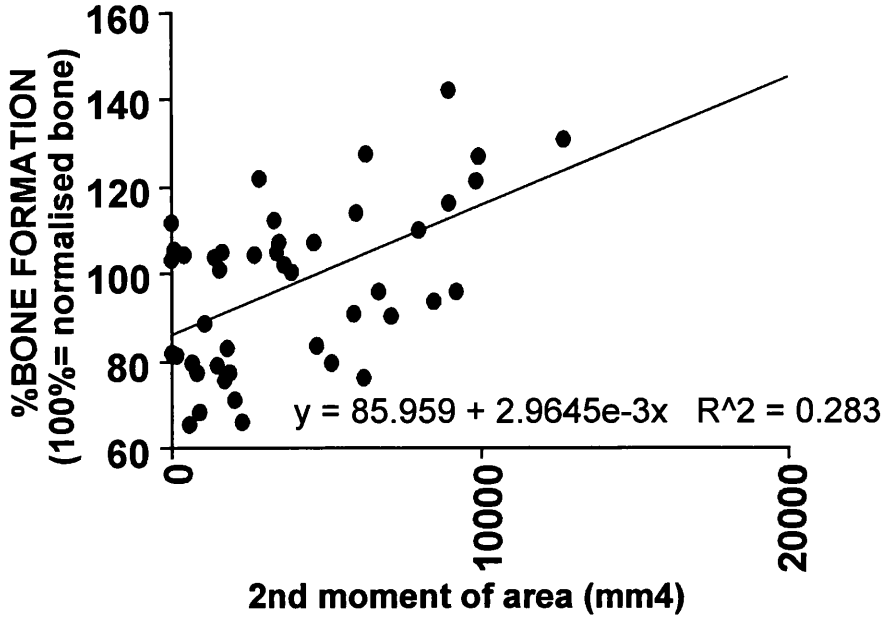


Figure 27a: A graph showing the correlation between bone formation and I in the AP aspect.

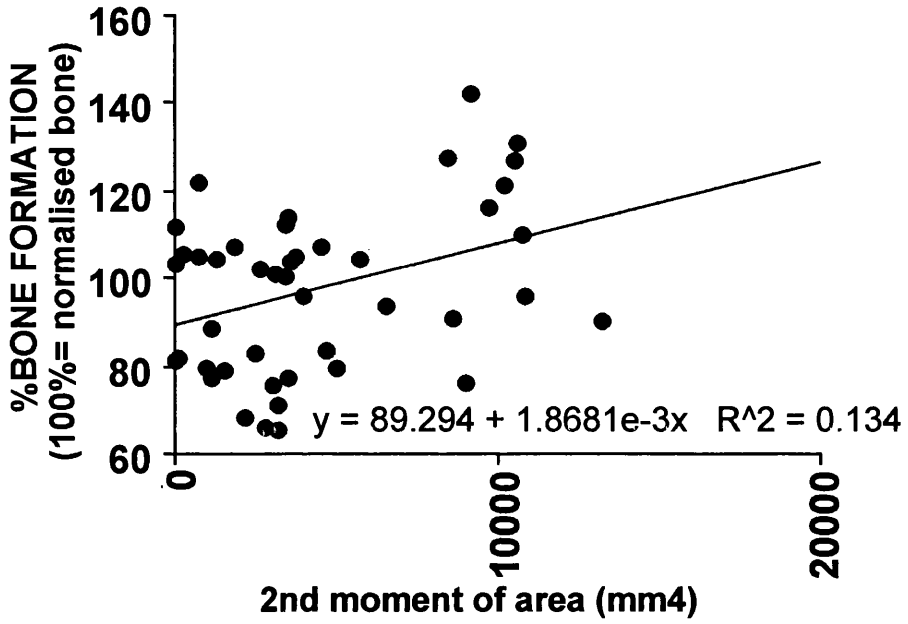


Figure 27b: A graph showing the correlation between bone formation and I in the ML aspect.

4.4 DISCUSSION

Bone is capable of aligning and adjusting its mass, texture and shape by a process of remodelling in response to mechanical stress. Contact radiographs of serial slices and measurement of the second moment of area showed that there were changes in the cross-sectional area of the plated tibia. The second moment of area can be related to the flexural stiffness and to strain. In our study bone was maintained even though the stiffness of the bone-implant composite increased. Disuse osteoporosis is evident after the insertion of implants and research has generally attributed this bone loss to a reduction in stress. Results from my study showed how significantly increased cortical porosis occurred in bone adjacent to the stiffer 6 plate implant design. Significantly less cortical porosis was measured in bone adjacent to the more flexible 2 plate implant design. My study also showed significantly less cortical porosis in bone at the more flexible tips of the plates when compared with the stiffer distal regions. In addition, my results using image analysis showed that more bone had formed adjacent to the 6 plated implant and least around the 2 plated design when compared with average values taken from the unoperated limb. An *in vivo* study (Schatzker *et al.* 1978) reported an 80% reduction in bone strain following extra-cortical plate application. The greatest reduction was seen directly beneath the plate. A recent finite element analysis study performed by Teman, 1998 (personal communication) investigated massive bone tumour fixation using extra-cortical plates in the human model. This study examined extra-cortical fixation to the proximal femur and compared a 2 and 3 extra-cortical plated implant model. The study also varied the length and thickness of the plates.

Remodelling changes in bone have been related to changes in the strain energy density (SED) (Huiskes and Verdonschot, 1997) and suggests that bone recognises minimum and maximum strain energy thresholds which switches bone formation on or off. In order for bone formation to be initiated, a minimum strain energy must be seen by bone.

The study performed by Teman concluded that the SED seen by bone following extra-cortical plate fixation was not enough to encourage bone formation around the plates. In addition, he reported that the SED was not uniformly spread in bone under the plate. However, there were areas where the SED did increase above the threshold and these were typically at the ends of the plate.

Our study demonstrated localised areas of bone formation and resorption along the plated tibia suggesting localised areas of increased load and stress protection respectively. This was particularly evident in the stiffer implant designs. In these cases, significantly more bone had formed around the implants when compared with the unoperated tibia, however, increased bone formation was associated with increased amounts of osteoporosis.

Teman concluded in his study that in order to encourage bone formation in response to plate fixation, it was important to try and increase the load seen by the bone. He proposed three methods:

1. Modifying the plate geometry;
2. Modifying the plate composition;
3. Modifying the bone.

Woo *et al.* 1976 studied the effect of plates with large differences in bending stiffness and examined the effect that this had on osteoporosis. They found, as was found in our study, that the more rigid plates induced most osteoporosis. Tibial sections in our study illustrated that osteoporosis occurred more in the distal regions where the implant was stiffest. In the proximal regions the plates were incorporated into remodelled cortical bone and there was little porosis. When comparing the different designs the least osteoporosis was seen in response to the 2-plated design that had the lowest bending stiffness. Therefore, by making the plates more flexible, more load is seen by the bone which may reduce the incidence of disuse

porosis. The flexibility of the extra-cortical plates can also be increased by manufacturing plates of reduced thickness (<1mm). In our study, the plate thickness was reduced from the shaft to the tip making the plates more flexible proximally. Most osteoporosis was seen distally while plate integration within the cortical bone (with little porosis) was demonstrated proximally. However, by reducing the thickness of the plate the mechanical integrity of the plate is also reduced. An extra-cortical plate must be manufactured to survive the mechanical load regimes imposed on an implant during all activities.

Studies have suggested that the porosis observed beneath extra-cortical plates was induced by necrosis caused by interference with the blood supply. It has been shown that external plates do interfere with the periosteal blood supply causing local bone ischemia (Perren *et al.* 1988). However, another study failed to find any correlation between cortical necrosis and consequent cortical porosis (Uhthoff *et al.* 1994). The implants used in our study had slots manufactured into the plates to increase the flexibility of the plates and to aid revascularisation. Our results demonstrated how bone growth significantly increased in response to the slotted plate when compared to bone growth around the unslotted plate. Our study also demonstrated how bone turnover rates were highest as bone grew into a slot.

A study (Akeson *et al.* 1976) measured cortical thickness in the presence of internal fixation plates and showed that rigid plate fixation resulted in a thinning of the cortex associated with a reduction in the structural strength of the bone. In our study the attachment of 2 extra-cortical plates onto the tibia induced a significant reduction in total bone area when compared to the contralateral limb. Qualitative analysis demonstrated a reduction in the cortical thickness of the sections accompanied with an increase in girth. A reduction in porosis was also observed. This was in contrast to the 3 and 6 plate designs. There was no significant difference in 2nd moment of area

between the left and right tibiae in the 2 plate design suggesting that the bone had altered its structure in order to match the changed loading conditions. In accordance with our study, Teman, 1998 suggested that a thinner cortex would increase the SED seen by that bone. He proposed that a thinner cortex would increase bone formation and reduce porosis.

A consequence of using rigid plates in combination with HA is the reduction in mechanical integrity of the HA coating. In our study we demonstrated hydroxyapatite particles in the soft tissues adjacent to the implant. We also observed delamination of the coating. However, all implants in our study remained stable throughout the 6 months and the plates became surrounded by bone and all were incorporated into the load-bearing structure of the tibiae.

When comparing the different implant designs, the 2-plate design appeared to induce the least changes when compared with the unoperated tibia. This was measured in terms of bone growth, osteoporosis and adverse alterations in the mechanical properties of the tibia.

Figure 26 is a radiograph of a distal femoral bone tumour revision case. The young patient was treated using extra-cortical plates. The remnants of the previous cemented fixation can still be seen. At this time, the plates had been *in vivo* for a year and 4 months and it can be seen that there were no apparent adverse effects. The fixation is stable and presently the patient reports no discomfort. Extra-cortical plates were used to fix a distal femoral prosthesis to the remaining short segment of bone. This case highlights the success that can be achieved when using extra-cortical plates to fix these implants to bone.

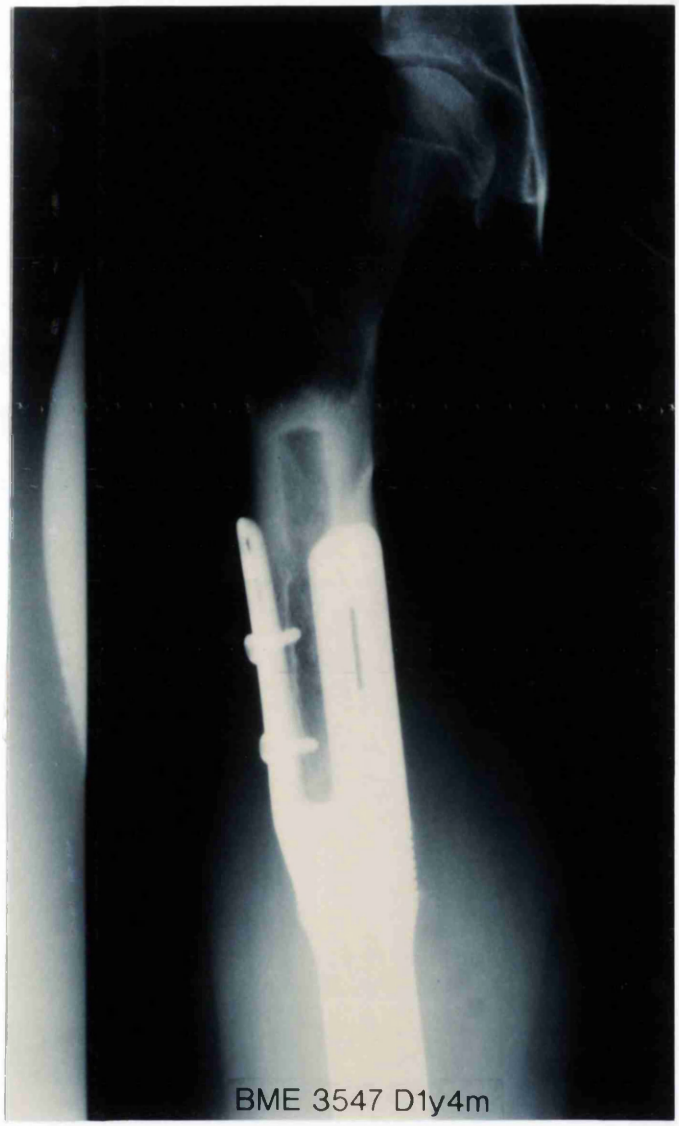


Figure 26: A radiograph of a distal femoral massive prosthesis attached by extra cortical plates. The patient reports no problems.

We have concluded from this study that extra-cortical plate fixation which relies on the local mechanical environment for the simulation of bone growth to incorporate prostheses into the load bearing structure of the bone, offers an alternative method for the fixation of segmental bone tumour implants, particularly for patients requiring revision prostheses and where implants are to be fixed into short segments of bone.

Chapter Five

A COMPARISON OF BONE REMODELLING AROUND HYDROXYAPATITE COATED, POROUS COATED AND GRIT BLASTED HIP REPLACEMENTS RETIEVED AT AUTOPSY

5.1 HYPOTHESIS AND INTRODUCTION

Chapter three of my thesis investigated various HA coatings and uncoated surfaces and the response of bone to these uncemented implants. It concluded that a crystalline hydroxyapatite coating was beneficial in terms of encouraging bone attachment to the implant surface. As with many scientific studies, my study investigated bone attachment and ingrowth in the rabbit model. The aim of this chapter was to investigate the response of bone to the uncemented interface in the human situation. This chapter hypothesised that a crystalline HA coating would have beneficial effects in terms of encouraging maximal amounts of bone ingrowth and attachment to the uncemented implant surface. Bone ingrowth and attachment to a HA coated porous titanium surface, an uncoated plain porous titanium surface and a grit blasted titanium (Interlok) surface were investigated in one femoral design from specimens obtained at human autopsy.

Several reports investigating the clinical outcome obtained after the insertion of porous-coated uncemented implants into patients have demonstrated good results (Engh, 1983; Engh *et al.* 1987; Hedley *et al.* 1987; Callaghan *et al.* 1988). Most studies found some degree of bone ingrowth (Brooker and Collier, 1984; Bobyn and Engh, 1984; Cook *et al.* 1988; Cook[a] *et al.* 1988; Jasty *et al.* 1988) with the mean extent reported to be in the range of 5% (Cook *et al.* 1988; Cook[a] *et al.* 1988) to 40% (Jacobs *et al.* 1989) of the available pore volume. Plasma coated hydroxyapatite is commonly used to modify the uncemented implant surface prior to insertion into a patient. Many animal studies as well as human retrievals have demonstrated the osseoconductive properties of hydroxyapatite and clinical results at 6 to 8 years are excellent (D'Antonio *et al.* 1992; Geesink, 1993). Bone apposition appears to be well advanced as early as 3 weeks (Bloebaum, 1991; Hayshi, 1991) and in some studies, HA has shown a greater than 90% bone apposition at 96 weeks (Hayashi, 1991). There is concern that HA resorbs with time and that the release of HA debris may cause adverse effects,

especially at the articulation (Donath, 1990). Many studies have suggested that these factors may cause early implant loosening. However, the clinical results reported so far for HA-coated components suggest that this is not at present a significant problem (D'Antonio[a] *et al.* 1992; Geesink, 1993).
Several studies have examined the use of a hydroxyapatite surface coating on porous coated implants. Some of these studies have reported no clinical advantage in the use of hydroxyapatite (McPherson *et al.* 1995; Spector, 1987), while others have demonstrated a significant increase in bone ingrowth following the application of a HA coating (Ducheyne *et al.* 1988; Moroni *et al.* 1992).

This study investigated the effectiveness of a hydroxyapatite coating in terms of increasing the amount of bone ingrowth and attachment to the implant surface. This study also examines the effect of HA in creating a more even bone distribution over the implant surface. This may have implications for reducing stress shielding and for limiting wear particle induced osteolysis.

5.2 MATERIALS AND METHOD

One hundred and sixty-five patients with an average age of 84.8 years (range 79 - 92yrs) were treated for a fractured neck of femur with a Bimetric hip hemi arthroplasty (Biomet Ltd, UK) at the Basingstoke General Hospital, Hampshire. Each patient randomly received a femoral component with *either:*

1. A plain porous (non-HA coated porous) surface,
2. A porous HA (HA coating on porous structure) surface
3. A grit blasted titanium surface (non-HA coated).

These coatings were applied onto the proximal region of the femoral stem. All of the porous titanium coatings were applied to the implant surface using a plasma spray process. The hydroxyapatite coatings were also applied by the plasma spray process and had an average crystallinity value of >85% and an average thickness of 50μm. The grit blasted titanium surface (Interlok) had a Ra value of 6μm. All of the coatings were developed and applied by Biomet Ltd, UK). Prior to surgery, permission was sought from patients and their next of kin to retrieve the implants upon their death. The implants and associated femora were collected at autopsy *(fig. 1)*.

Fifty-eight autopsy specimens have been retrieved;

15 Interlok specimens (duration 4 - 938 days (2.5yrs)),
24 porous coated specimens (duration 2 - 1572 days (4.5yrs))
19 hydroxyapatite coated specimens (duration 2 - 1057 days (2.8yrs)).

In this chapter, eight plain porous coated specimens; seven porous HA coated specimens and six Interlok specimens were analysed. The duration

of these implants was matched as far as possible and ranged from 38 days to 4.5 years.

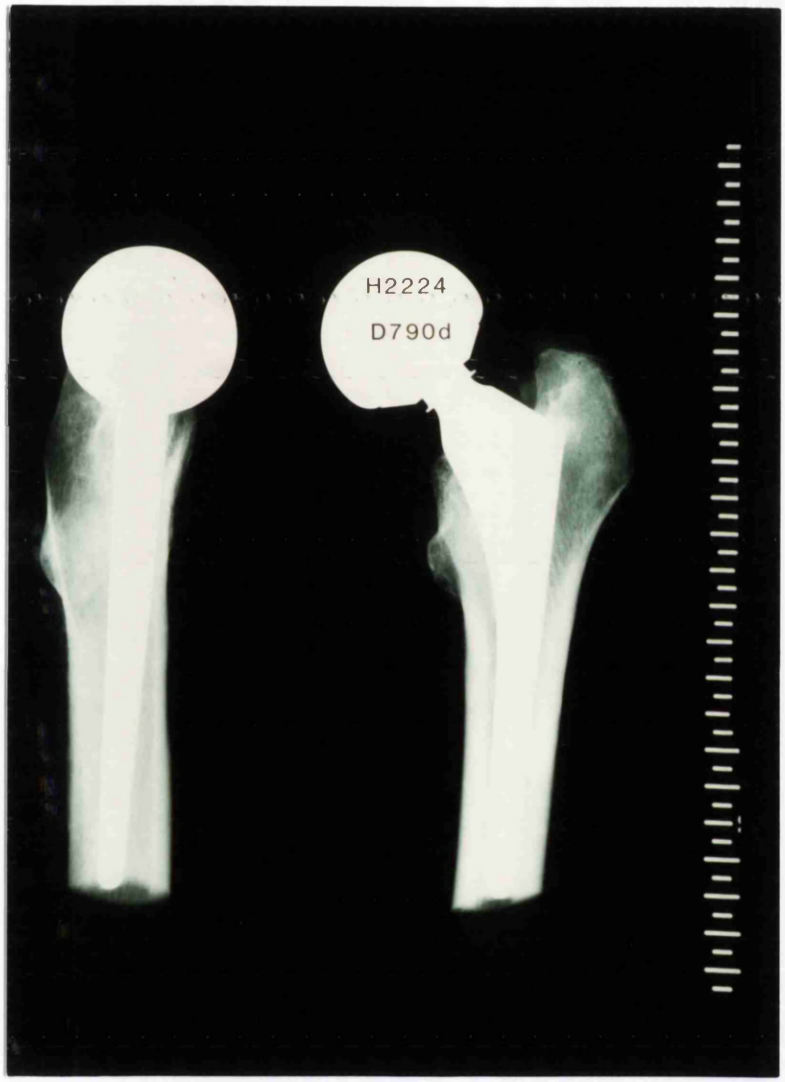


Figure 1: A radiograph of a retrieved Interlok specimen (790 days duration).

On retrieval the specimens were fixed in buffered 10% formaldehyde solution and excess soft tissue was removed. The proximal region of each femoral component (i.e. the coated area being investigated) was cut using an Exotom cut off machine (Struers, UK), into a proximal (F1), mid region (F2) and distal region (F3) *(fig. 2)*.

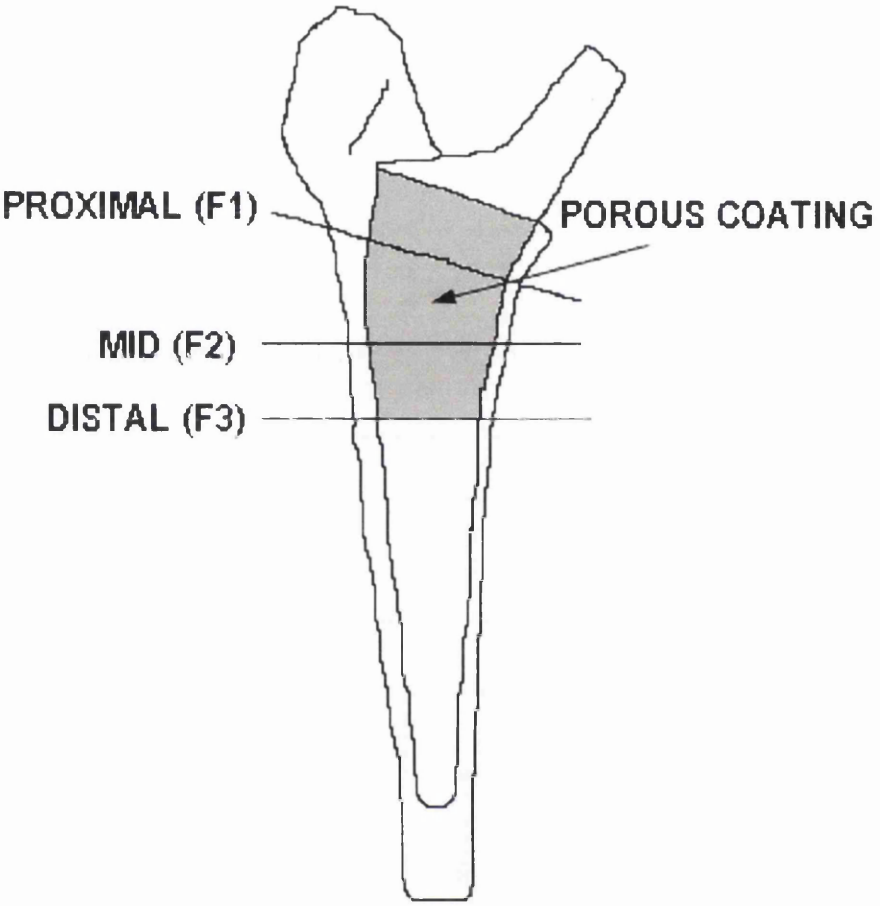


Figure 2: A schematic diagram showing areas investigated.

Once sectioned the specimens were prepared for hard tissue processing. Sections were dehydrated in serial dilutions of alcohol (30%, 50%, 70%, 90% followed by absolute alcohol). Immersion in chloroform resulted in fat clearance before impregnation and casting in L R White hard grade acrylic resin. Thin sections (<50 μm) were prepared through each of the F1, F2 and F3 regions using a diamond saw and grinding and polishing techniques. An Isomet 2000 diamond saw (Buehler Krautkramer) was used to cut the sections and a Motopol grinding and polishing machine (Buehler Krautkramer) was used for thin sectioning and final polishing. Toluidine blue and Paragon were used to stain the soft tissue and bone respectively.

Following staining, bone ingrowth and the quantity of hydroxyapatite coating within the void volume of the porous structure was measured using image analysis. The % bone contact to each of the implant surfaces was measured using light microscope grid morphometry.

5.2.1 IMAGE ANALYSIS

Images from the microscope were captured onto computer using Neotech Image Grabber software (Graftek, 1988). Image analysis software using colour thresholding techniques (Optilab, (ME Electronics, UK)) was used to determine regions of interest. These regions were total pore area within the field of view, hydroxyapatite within the pores and bone ingrowth. All measurements were made through x10 magnification on the microscope. These regions of interest were converted into binary images and particle number was quantified. Bone ingrowth was quantified over the entire porous surface of each implant and was also quantified separately at the proximal, mid and distal regions of the coated area. Bone ingrowth was also measured and compared in the medial and lateral aspects.

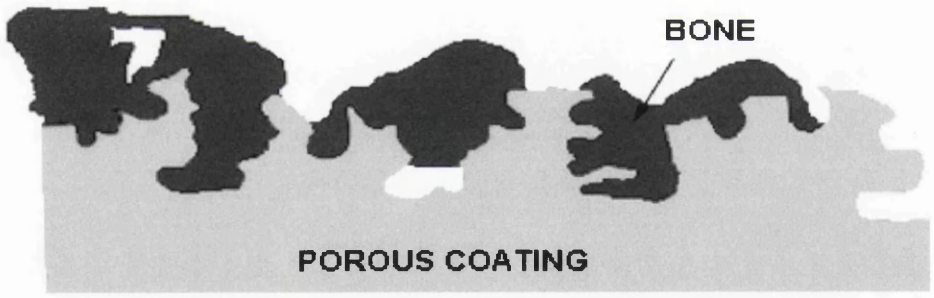


Figure 3a: The image is grabbed from the microscope.

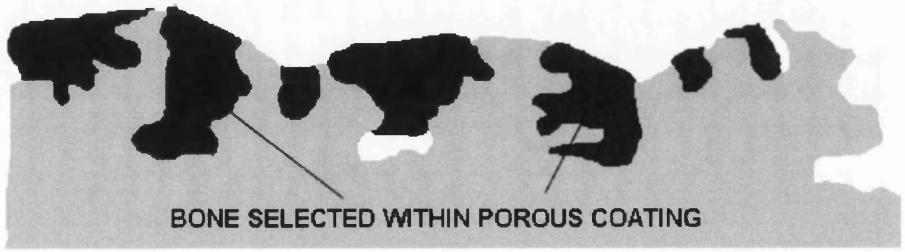


Figure 3b. Using image analysis software, the bone within the porous structure was determined.

BONE WITHIN POROUS STRUCTURE IS MEAURED

Figure 3c: A binary image was created and bone within the pores is measured. This method was repeated to quantify hydroxyapatite.

5.2.2 LIGHT MORPHOMETRIC ANALYSIS

Light micoscopy was used to measure bone attachment onto the outer surface of the implant. This was done using a line intercept method and Merz graticule demonstrated diagrammatically in figure 4 below.

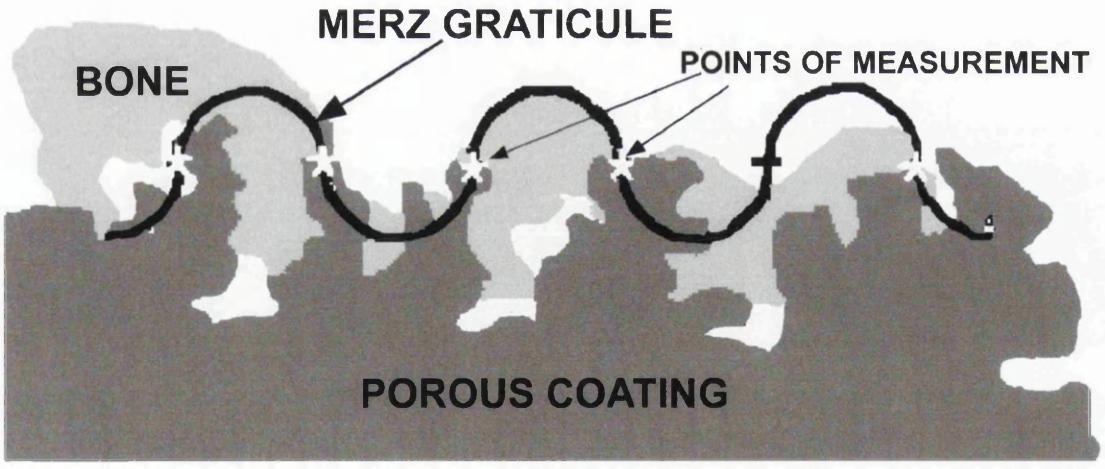


Figure 4: A schematic diagram demonstrating how the Merz graticule was used to measure bone at the interface.

This method of analysis was a repeat of that used in chapter two. The points at which the Merz line crossed the interface were observed and to

tissue type (bone or fibrous tissue) noted. Bone attachment to the implant was compared over the entire surface of the implant and at the three (F1, F2 + F3) levels.

5.2.3 STATISTICS

A normality test was used to determine whether the data was parametric or non-parametric. Results in this study had normality values >0.05 and therefore the students *t*-test was used for statistical analysis where values <0.05 were classified as significant.

5.3 RESULTS

Radiographs of retrieved femora demonstrated trabeculae streaming up to most of the porous coated and HA coated implants. Figure 5 is an example of a thin section through a plain porous implant and shows how bone trabeculae streamed up to the implant from the surrounding cortex. However, sections prepared through the Interlok specimens did not demonstrate streaming of bone trabeculae to the implant surface *(fig. 14)*.

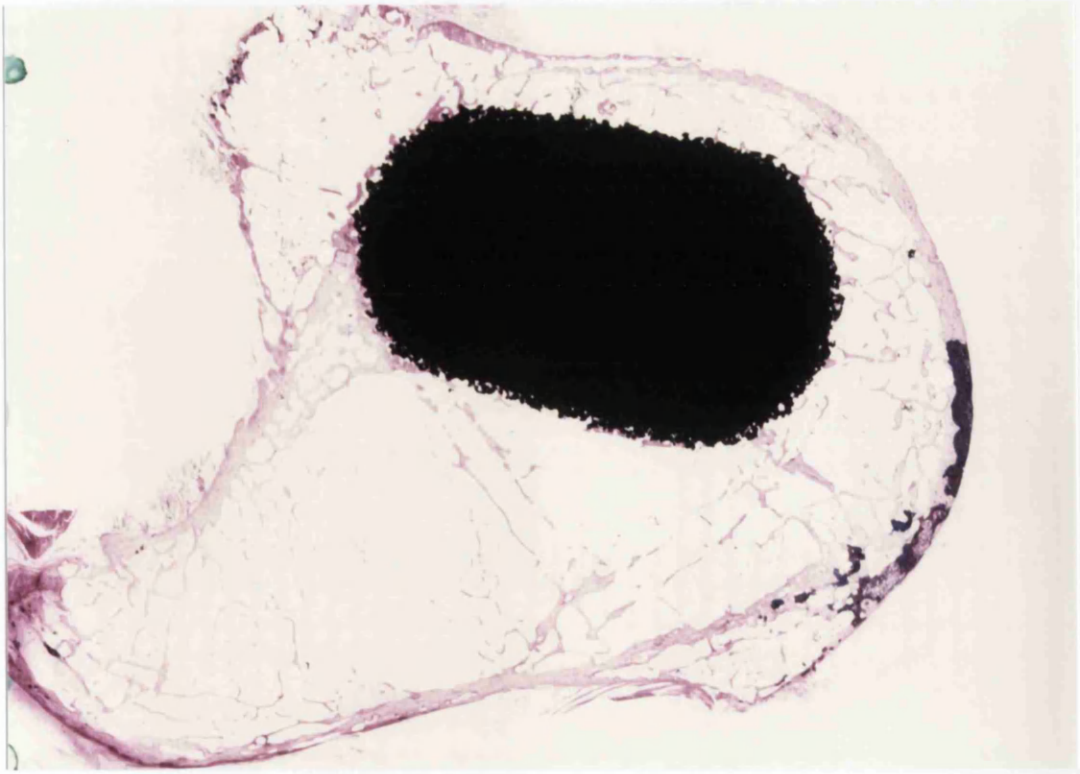


Figure 5: A section through F3 of plain porous specimen duration 1094 days.

Sections through all of the implants taken earlier than 6 months showed how bone particles and chips remaining from surgery formed a scaffold onto which new bone had grown and subsequently invaded the porous structure *(fig. 6)*.

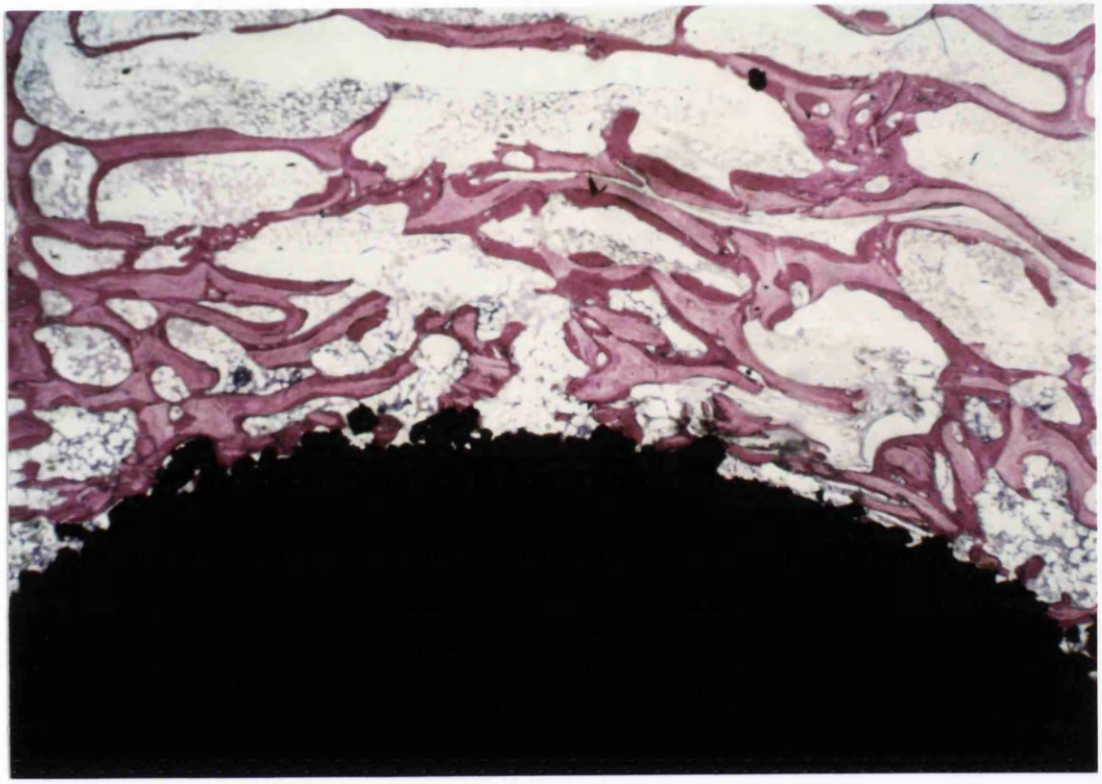


Figure 6: A photomicrograph showing particles of bone remaining following surgery forming a scaffold onto which new bone has grown.

Sections prepared through the femur of patients where the trabeculae and cortices appeared very thin indicating osteoporosis, demonstrated an abundance of bone ingrowth and attachment to the implant surface *(fig. 7)*.

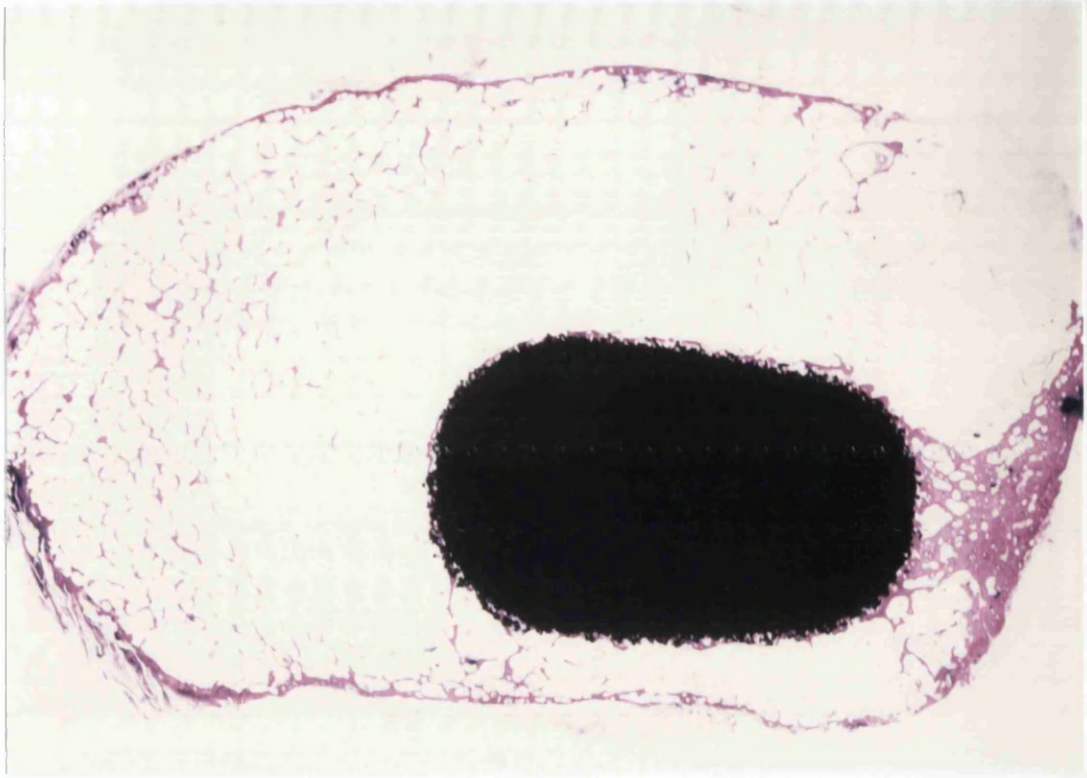


Figure 7: A photomicrograph showing growth to the implant in a section of osteoporotic bone.

5.3.1 BONE INGROWTH RESULTS

Results of bone ingrowth into the porous HA coating and plain porous implants when taken over all time periods showed that there was significantly more bone ingrowth into the porous HA structure when compared with the plain porous surface (p=0.012) *(fig. 8)*. Light microscopy identified bone ingrowth into both the porous HA and plain porous structures *(figs. 9, 10)*. Image analysis techniques measured bone ingrowth and an average of approximately 30% of the void volume of the porous HA structure was occupied by bone compared with 21% for the plain porous coated implants.

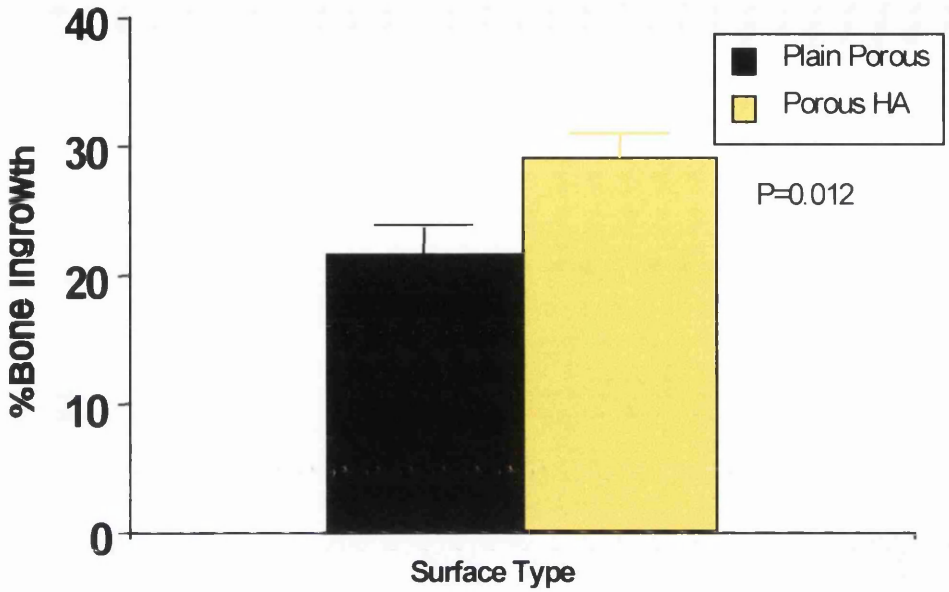


Figure 8: A comparison of % bone ingrowth to a plain porous surface and a porous HA surface (F1, 2 and 3; All durations).

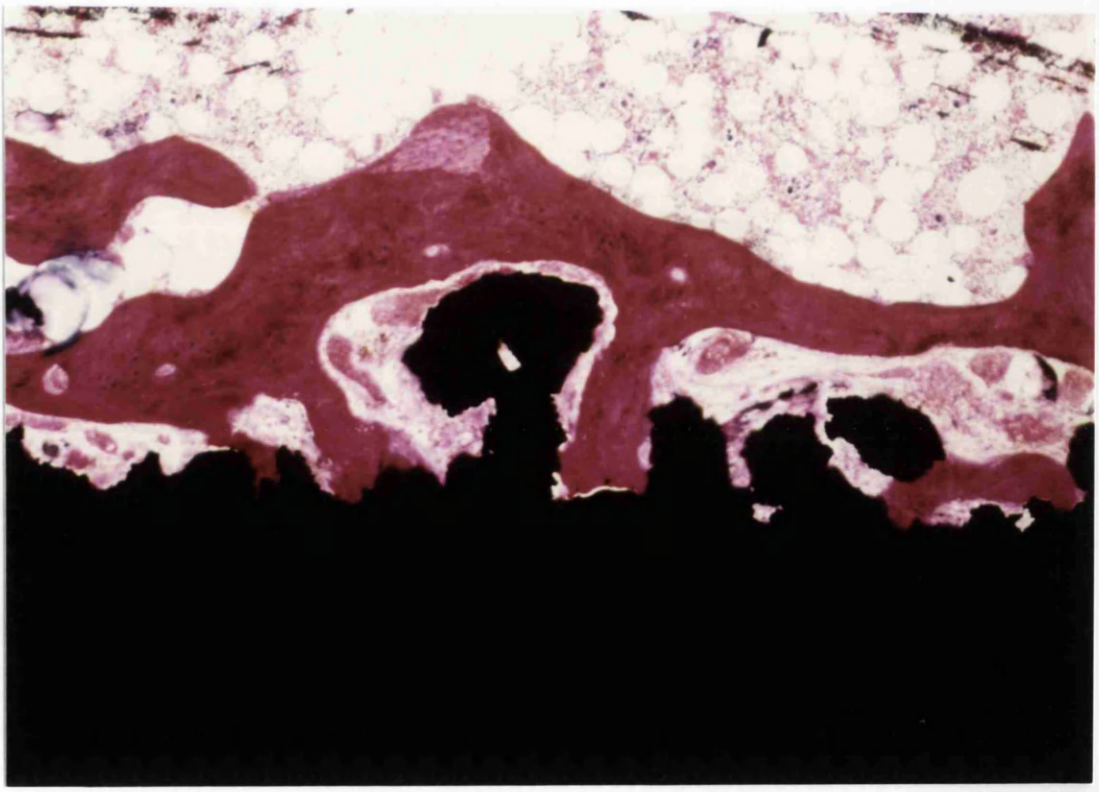


Figure 9: A photomicrograph showing bone growth into the plain porous surface (Mag x10).

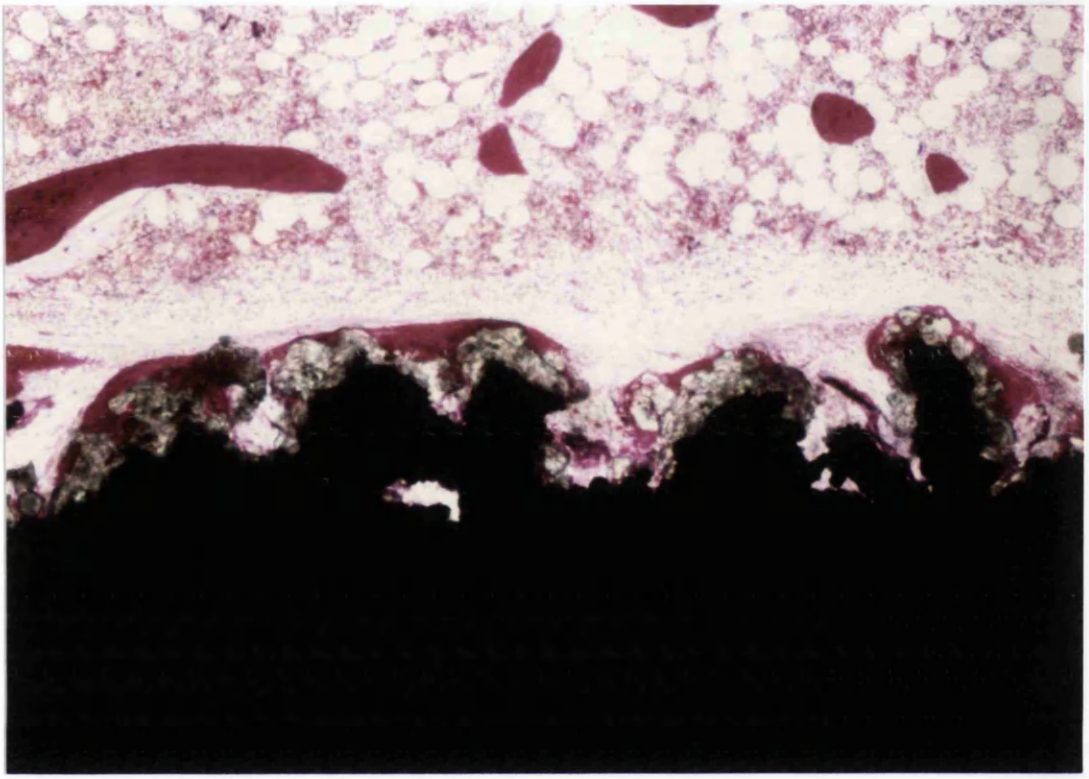


Figure 10: A photomicrograph of bone growth into the porous HA surface (Mag x10).

There was an uneven distribution of bone ingrowth into the plain porous coated implant surfaces with significantly more bone found in the distal region (30.48%) of the coating than in the proximal region (19.49%) (p=0.046). Also, significantly more bone ingrowth was demonstrated in the distal region of the plain porous coated implant compared with the mid region (p=0.001) (F1 and F2 p=0.524).

In comparison, bone ingrowth into the porous HA coated regions was more evenly distributed and no significant differences were found in bone ingrowth at the three levels (F1 and F2 p=0.618; F1 and F3 p=0.711; F2 and F3 p=0.934*) (fig. 11)*.

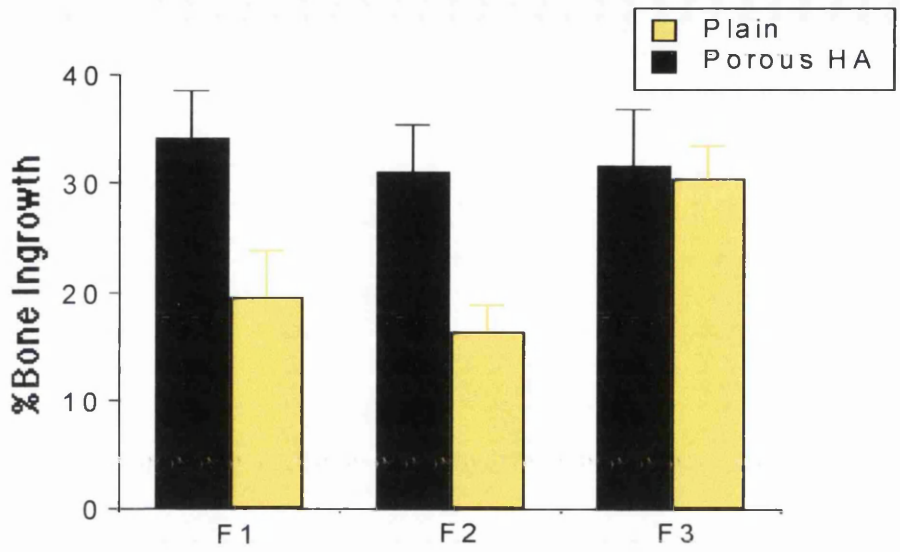


Figure 11: A comparison of % bone ingrowth into a plain porous and porous HA surface at the F1, F2 and F3 levels.

A comparison of bone ingrowth into the plain porous surface and the porous HA surface was also made in the medial *(fig. 12)* and lateral *(fig. 13)* aspects. Results demonstrated that with both porous surface types, most bone ingrowth was seen in the medial aspect *(fig. 14)*. Increased bone was also apparent in the Interlok specimens *(fig. 15)*. There was no significant difference in bone ingrowth between the HA and plain porous types in this aspect.

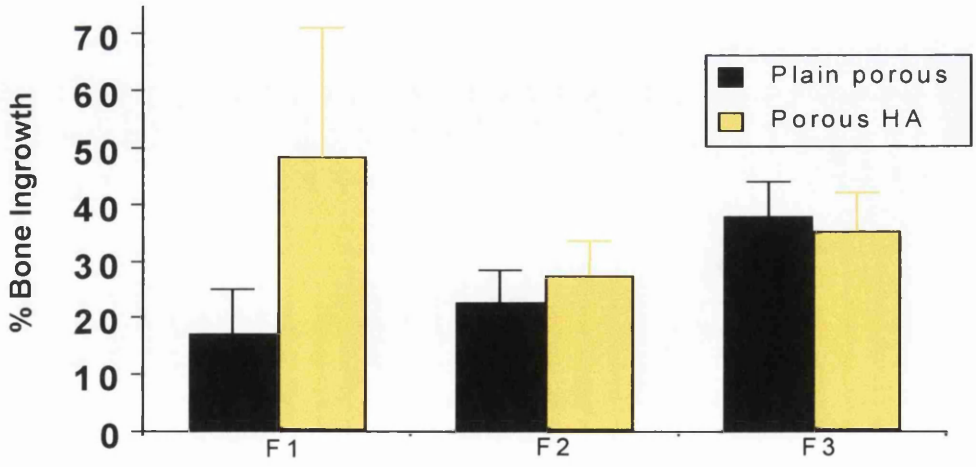


Figure 12: A comparison of % bone ingrowth in the F1, 2 and 3 regions in the medial aspect.

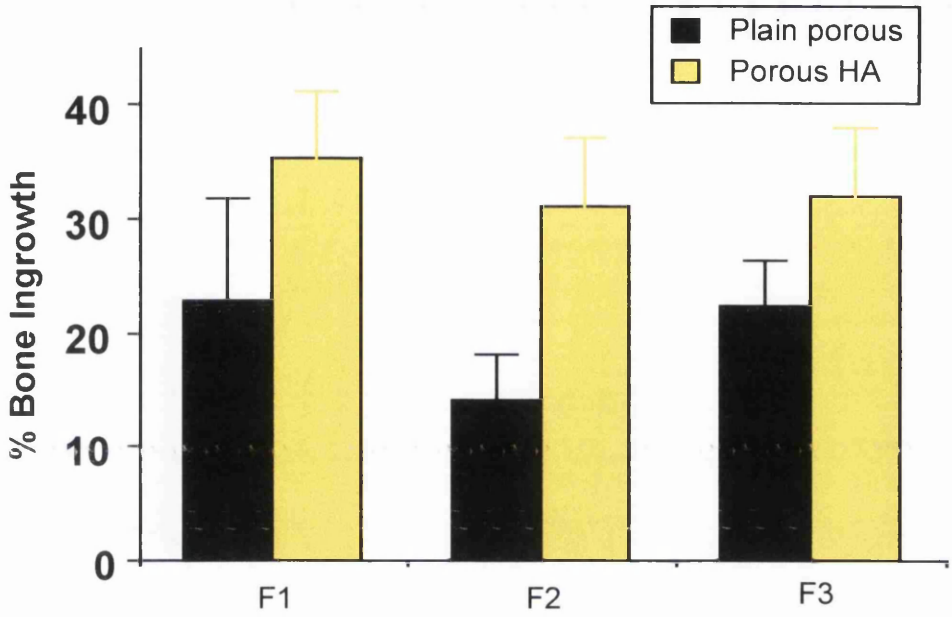


Figure 13: A comparison of % bone ingrowth into the regions F1, 2 and 3 in the lateral aspect.

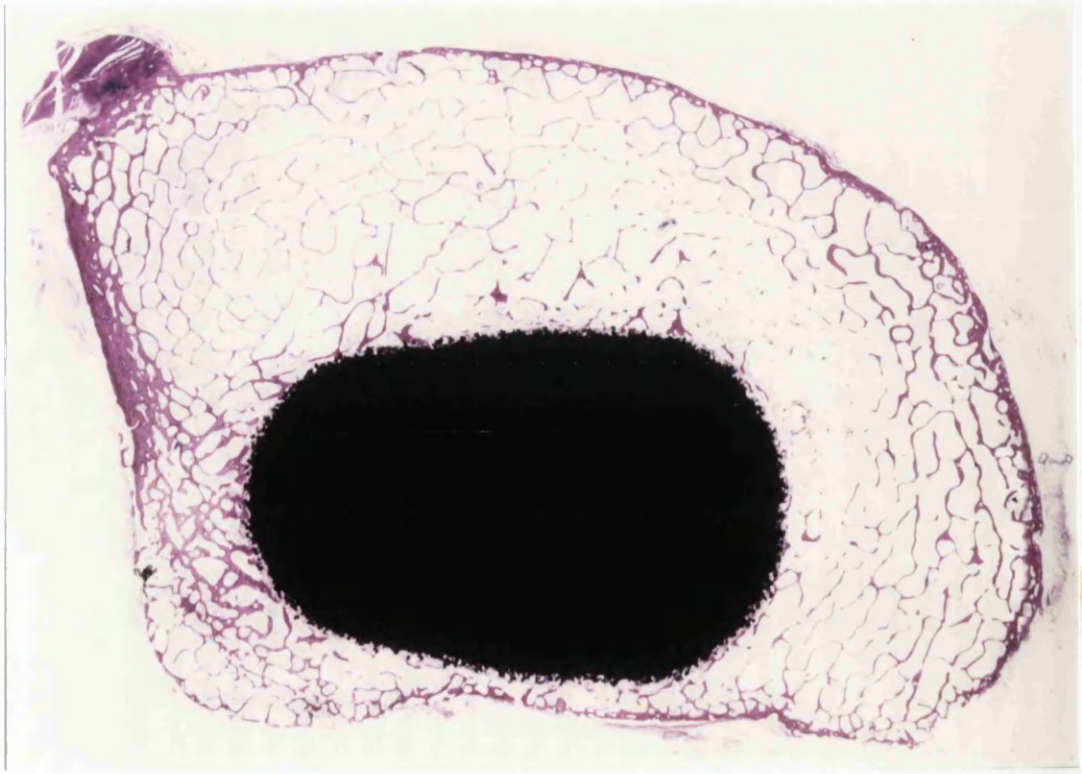


Figure 14: A thin section through a plain porous specimen showing increased bone growth in the medial aspect.

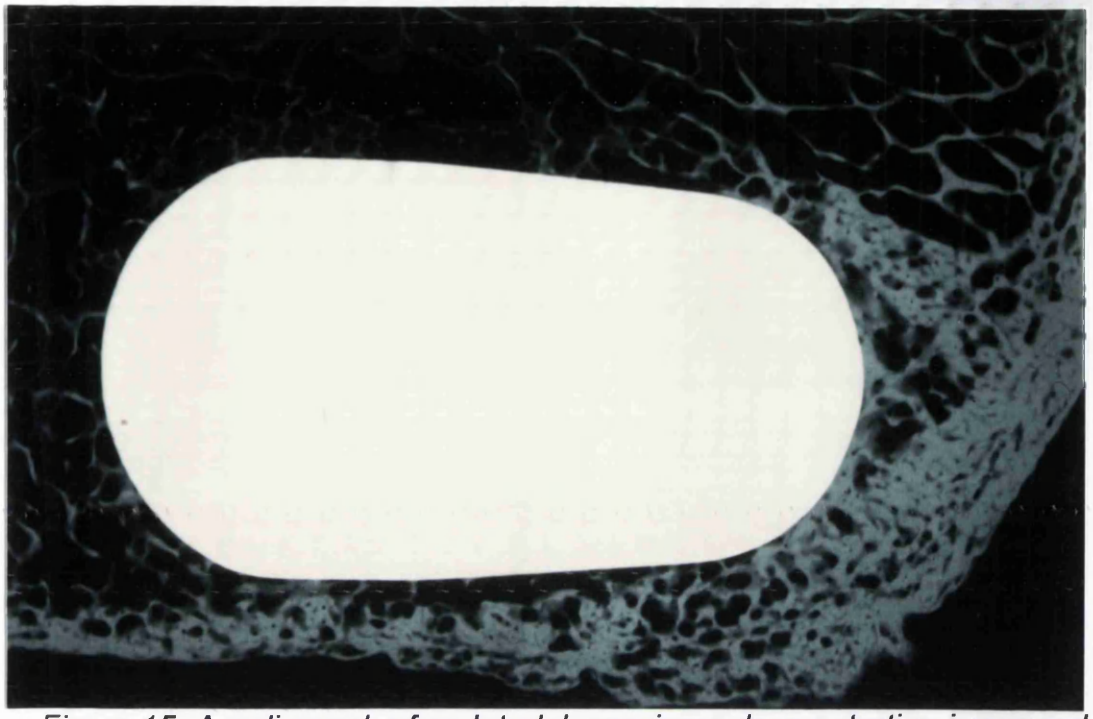


Figure 15: A radiograph of an Interlok specimen demonstrating increased bone growth in the medial aspect.

Figure 16 shows the relationship between bone ingrowth and the duration of the implant *in situ*.

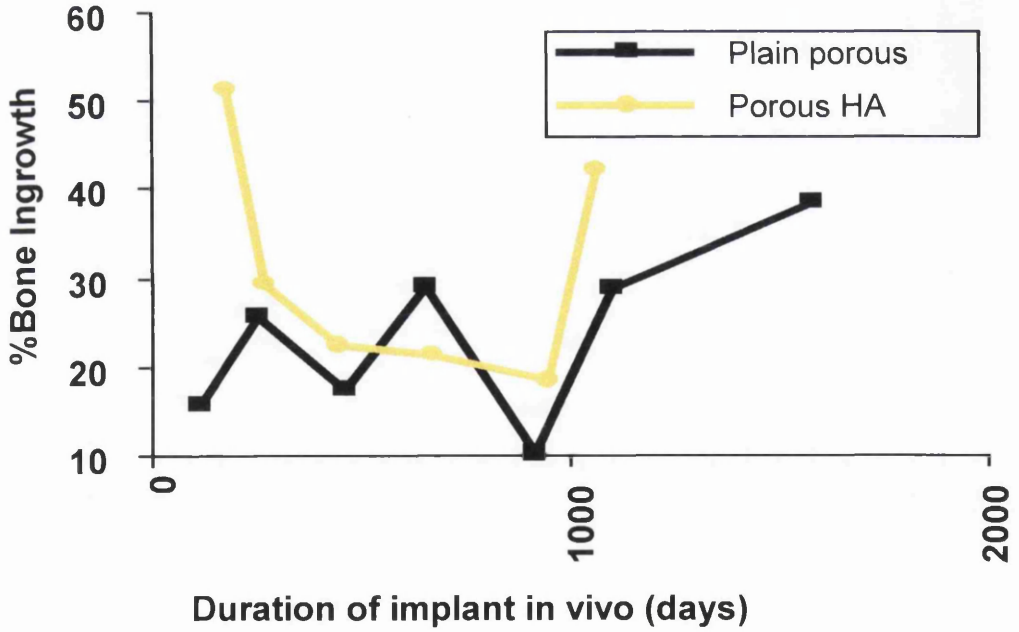


Figure 16: A graph showing the relationship between % bone ingrowth over time in the plain porous and porous HA surfaces.

5.3.2 BONE ATTACHMENT

Bone attachment onto the surface of the implants when taken over all time periods demonstrated that significantly more bone attachment had occurred onto to the porous HA coated surface when compared with both the plain porous coated surface (p=<0.05) and the Interlok surface (p=<0.05) *(fig. 17)*. However, there was no significant difference in bone attachment between the Interlok surface and plain porous coated implants (p=0.7).

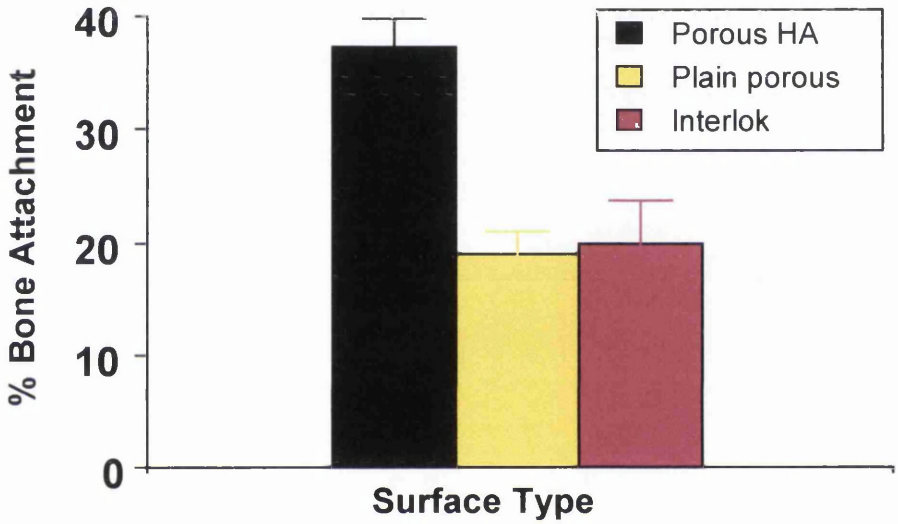


Figure 17: A comparison of % bone attachment onto a plain porous, a porous HA and Interlok surface (F1, 2 and 3. All durations)

Figure 18 demonstrates that bone attachment onto plain porous and Interlok surfaces was unevenly distributed and that most bone attachment occurred in the mid and distal regions of these implants. In comparison bone attachment onto the porous HA coating was more evenly distributed over the entire length of the coated area. There was no significant difference in bone attachment onto the HA coating at the F1, F2 and F3 levels (F1 and F2 p=0.671; F1 and F3 p=0.376; F2 and F3 p=0.538).

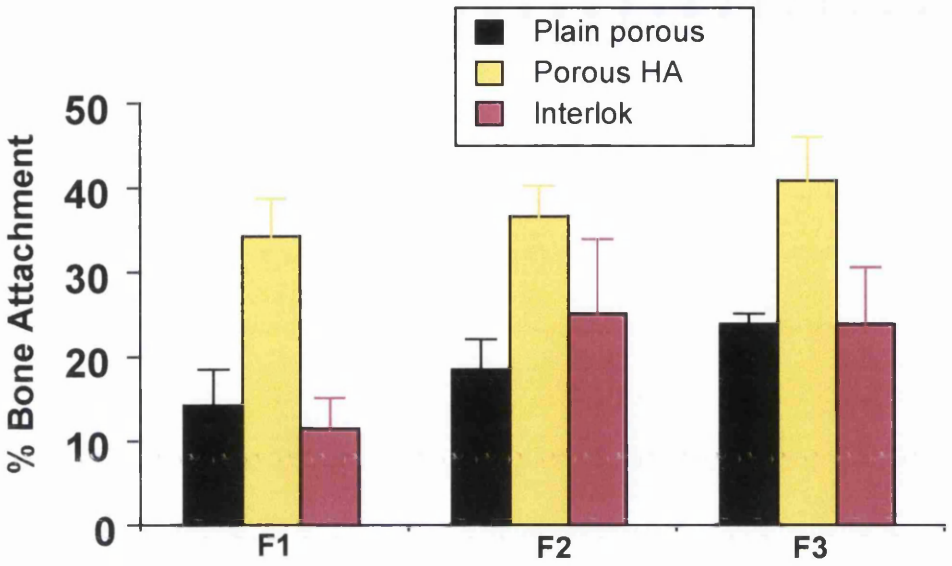


Figure 18: A comparison of % bone attachment on the plain porous, porous HA and Interlok surfaces at F1, 2 and 3 levels (all durations).

Figure 19 shows the relationship between bone contact and the duration of the implant *in situ*.

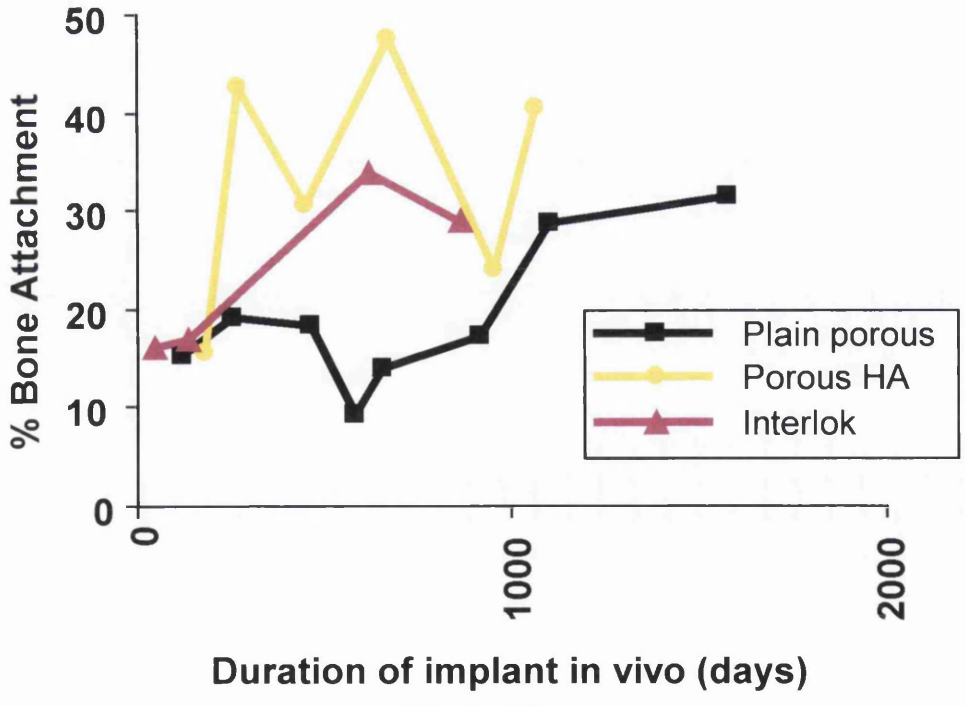


Figure 19.

Figures 20, 21, and 22, are sections through the proximal region of plain porous, Interlok and HA coated porous implants. These sections are from implants that have been time matched. The sections show how bone forms and grows into porous HA over the entire coated surface but in sections prepared through the plain porous implants at this level, there are large regions of fibrous tissue at the interface. Microscopic analysis of the Interlok specimens showed that in the majority of cases, the surface of the implant was interfaced with a well aligned layer of fibrous tissue *(fig. 23)*.

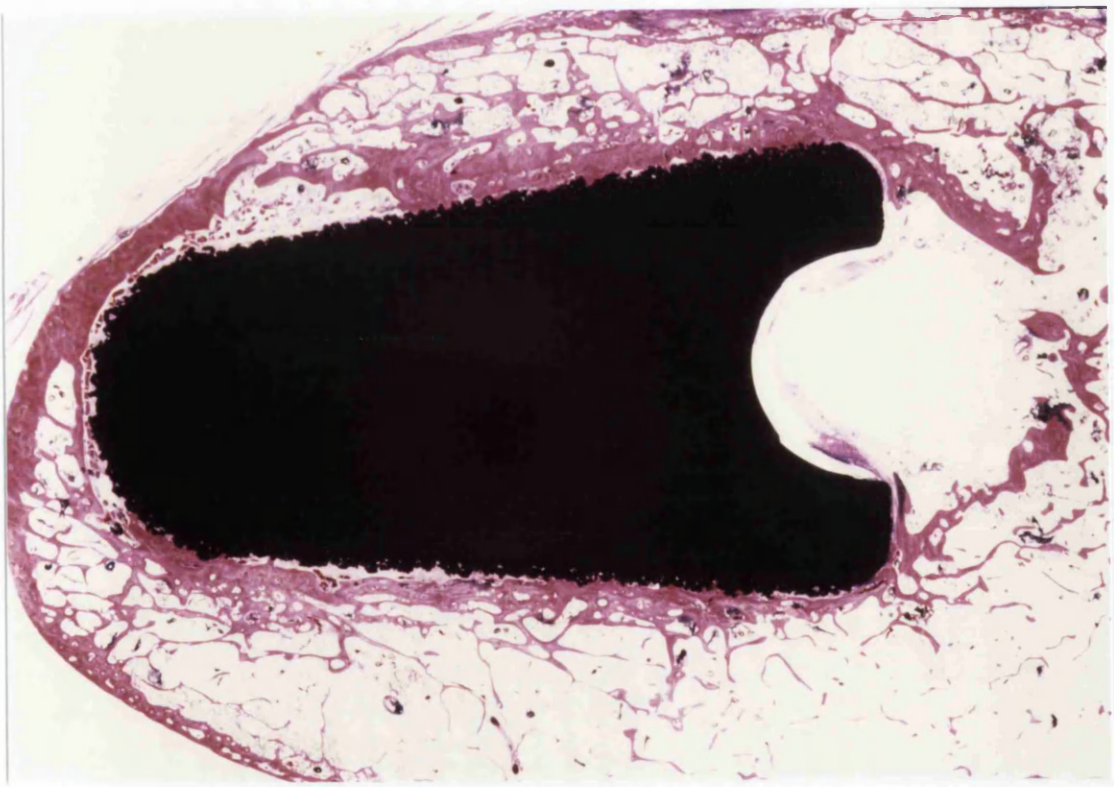


Figure 20: A section through the F2 region of a plain porous specimen.

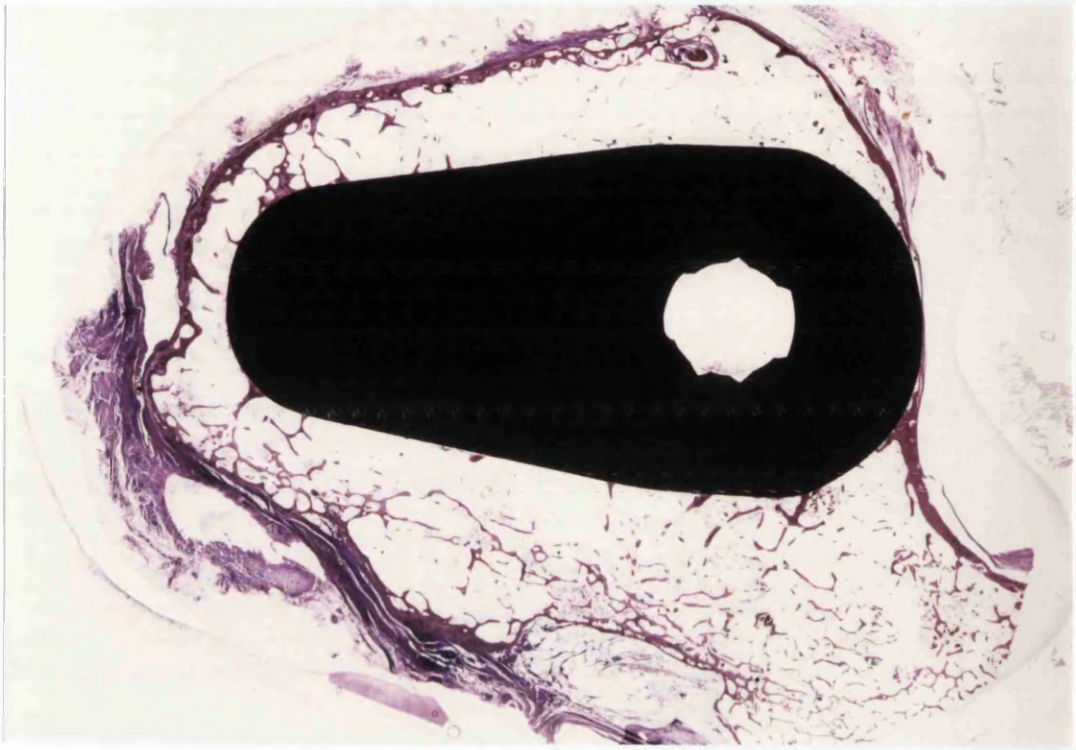


Figure 21: A section through the F2 region of an Interlok specimen.

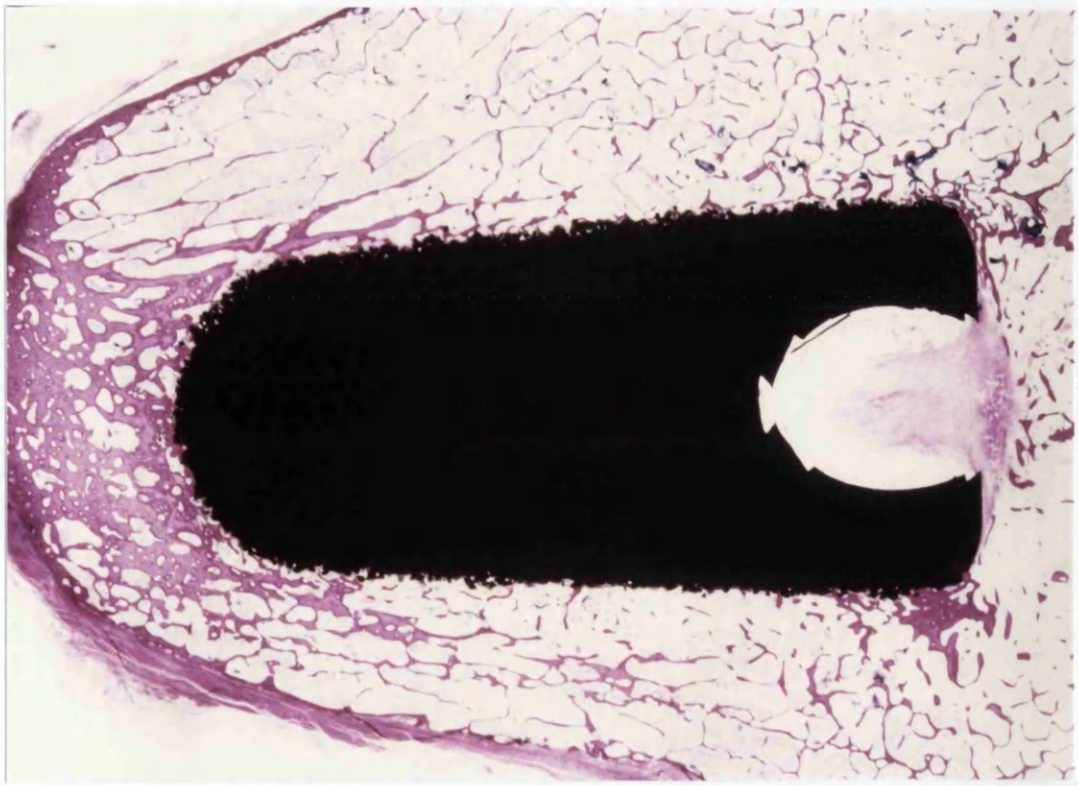


Figure 22: A section through the F2 region of a porous HA specimen.

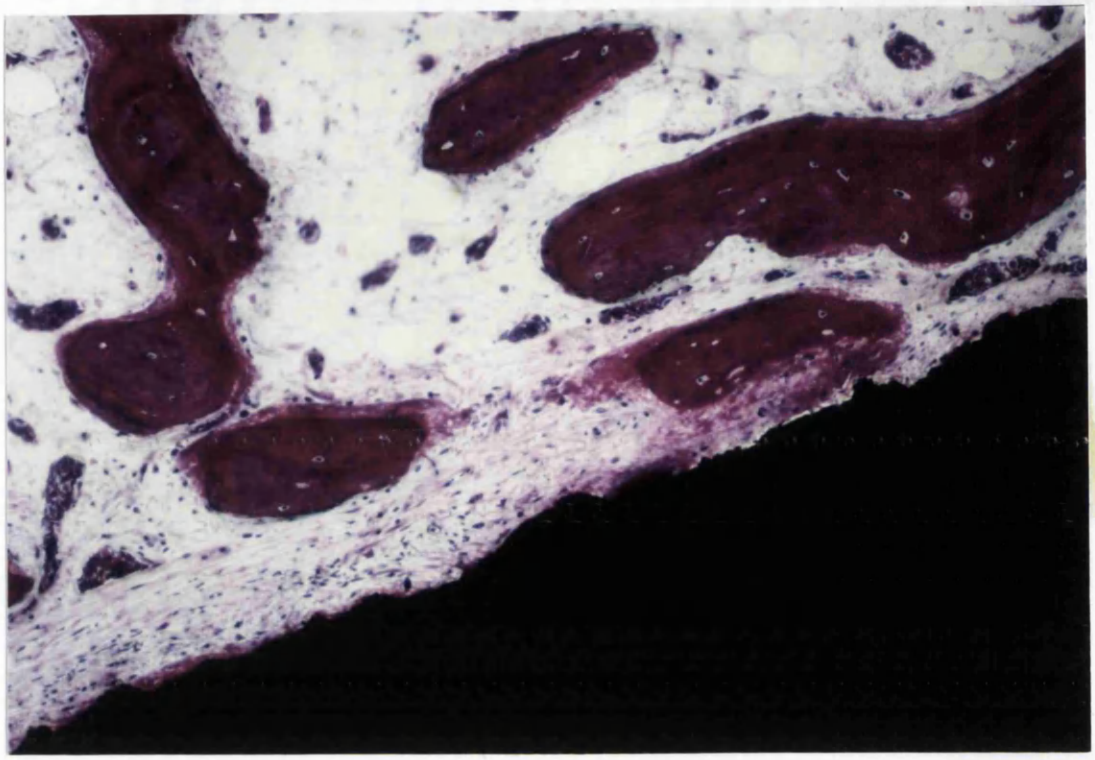


Figure 23. A photomicrograph of the bone-Interlok surface demonstrating how a layer of fibrous tissue separates the bone from the implant surface.

The ratio of bone attachment to bone ingrowth was greater on the porous HA coated surfaces than on the plain porous surfaces with bone forming preferentially along the surface of the HA coating when compared with the plain porous coatings *(fig. 24)*. Histology at the interface demonstrated that bone attachment and ingrowth occurred by different mechanisms when the porous HA and plain porous implant surfaces were compared. On the plain porous implant surfaces, pegs of bone had grown into the porous structure from a ring of bone that surrounded the implant. On porous HA specimens, bone formation appeared to be directed along the implant surface *(figs. 9,10)*.

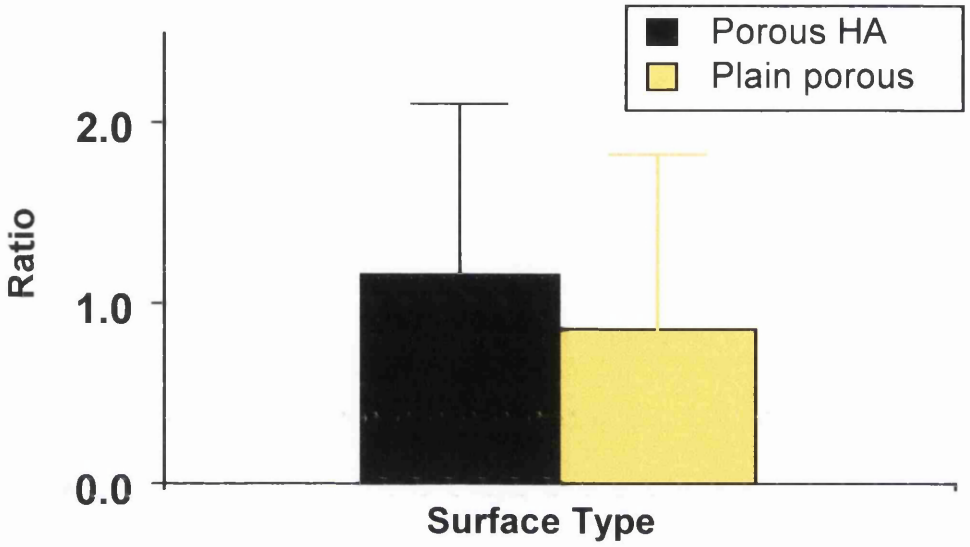


Figure 24: A graph demonstrating the ratio of bone attachment to bone ingrowth.

There was little quantitative evidence of HA coating degradation and no significant differences were found in the volume of HA on the implant surface when measured over time *(fig. 25)*. In some retrievals it was observed that the HA coating had broken up and less coating was present when compared with other specimens. HA particles were seen at localised areas around the interface and although these particles in some cases resulted in an inflammatory reaction, this appeared to have no effect on new bone formation or bone attachment to the implant. In other regions along the interface, HA particles were surrounded by bone *(fig. 26)*.

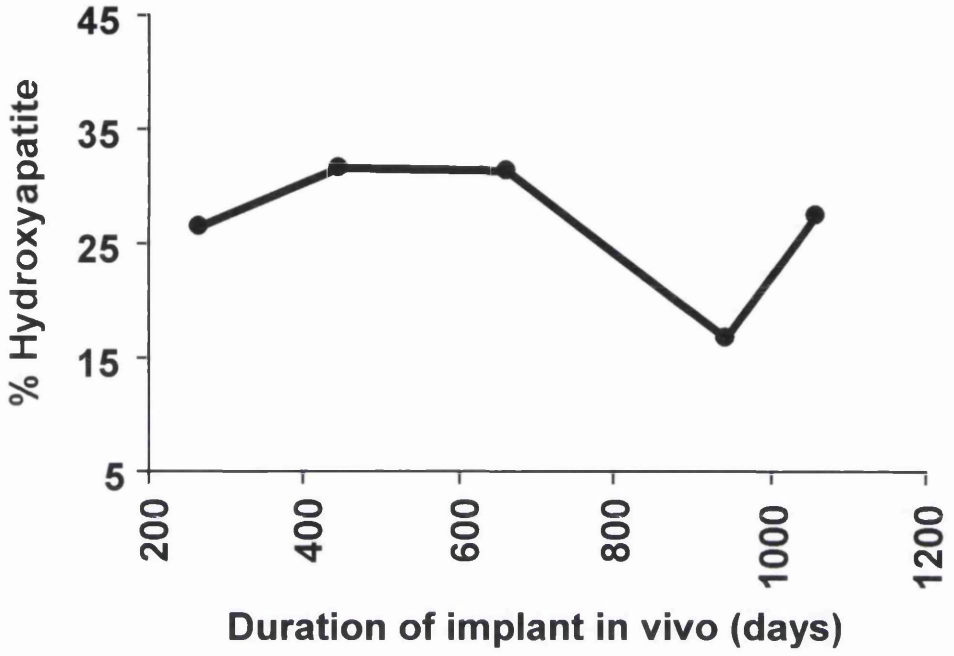


Figure 25: The relationship between % hydroxyapatite and the duration of the implant in situ.

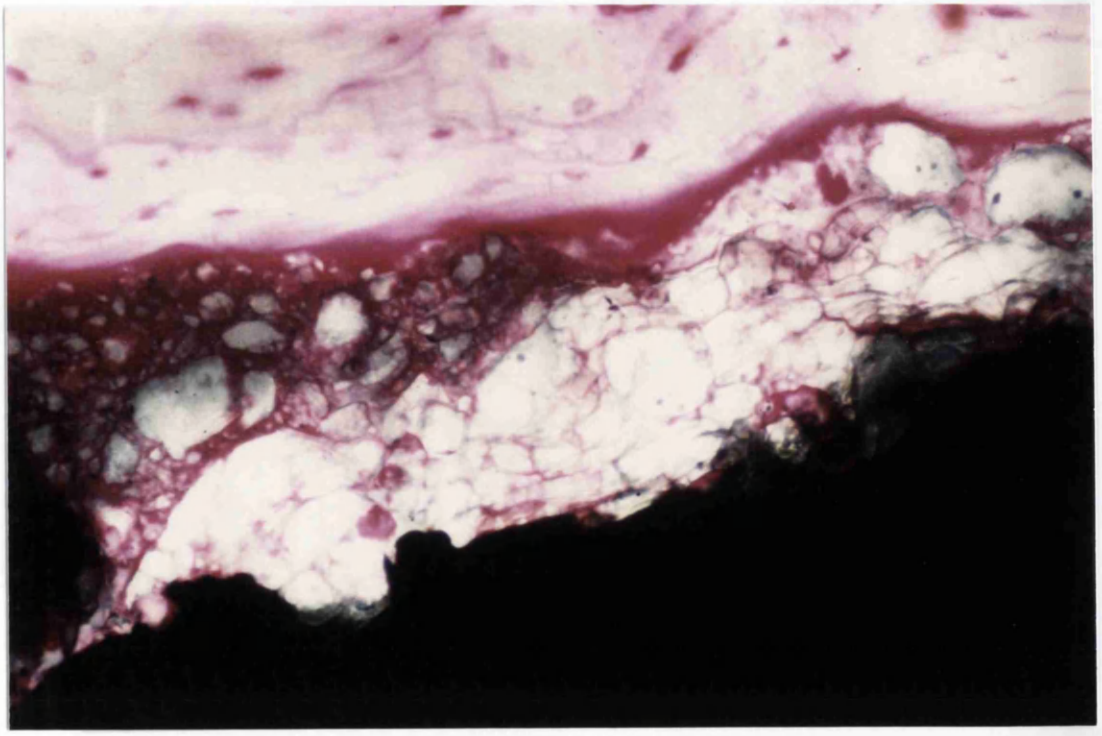


Figure 26: A photomicrograph showing fragmented HA particles surrounded by bone (Mag. x10).

5.4 DISCUSSION

This study has shown that in humans a hydroxyapatite coating significantly enhanced bone attachment and bone ingrowth into a porous surface. As has been shown in both human and animal studies bone ingrowth does occur into a plain porous surface (Brooker and Collier, 1984; Bobyn and Engh, 1984; Cook *et al.* 1988; Jasty *et al.* 1988;) however my study has demonstrated that the osseoconductive nature of HA significantly encouraged more bone to grow into and along the surface of the implant. Even in osteopenic bone, new bone formed along the surface in both the HA and plain porous implants. My study also demonstrated the importance of bone fragments left at the implant interface following surgery in that they provided a scaffold for the formation of new bone in that area. Quantification of bone around the plain porous and Interlok surfaces showed how our results compared favourably with figures for bone ingrowth into other porous coating systems (Cook *et al.* 1988; Cook[a] *et al.* 1988). My study demonstrated how bone formation was unevenly distributed in the proximal, mid and distal regions in plain porous and Interlok implants. More bone ingrowth and bone attachment had occurred in the distal region of the coatings and also in the medial and lateral planes when compared with the anterior - posterior plane. The distribution of bone around the HA porous coated type implants was more uniform with no significant differences between different levels or on any aspect of the implant. This may have significant effects in preventing wear particle migration along the implant interface by creating a uniform seal. It is possible that this more uniform bone attachment to the surface of the HA coating may also reduce proximal stress protection and subsequent bone resorption around the implant.

When the relationship between bone ingrowth and bone attachment onto the surface of the implant were examined over time it was evident that the responses to the HA coating appeared erratic. In one case bone attachment accounted for approximately 43% of the implant surface compared with 12%

attachment to an implant *in vivo* just a few months longer. This could be due to many factors such as the ability of the patient to form bone and to the surgical technique. Nevertheless, however erratic the response was to the HA coating, overall significantly more bone had grown into and attached to this surface when compared with the plain porous surfaces.

HA is thought to resorb over time (Donath 1990) exposing the metal surface beneath. In this study, the percentage of HA present in the porous structure was quantified. It was found that these values varied between each specimen however no significant differences in HA were calculated over the time periods examined. The HA coating had fragmented in some areas but appeared to have few adverse effects at the implant interface. A study performed by Bauer *et al.* 1991 investigated autopsy retrieved hydroxyapatite-coated femoral stems *in vivo* for an average of 12 months. He reported that bone had formed a uniform coating over the hydroxyapatite on each stem and that there was extensive direct bone apposition. However, he reported no evidence of HA fragmentation resulting in an inflammatory reaction. Several other studies have also investigated hydroxyapatite coated autopsy-retrieved components and all have reported early deposition and extensive bone formation onto the HA coating (Hardy *et al.* 1991; Soballe *et al.* 1991; Furlong, 1993). A clinical study was reported by Karrholm[a] *et al.* 1994, where the results for 60 hips of the same type were fixed with either cement, a hydroxyapatite coating or a porous coating. Their coatings were applied to the proximal one third of the surface. After 2 years the clinical results between the three types did not differ, however the HA coated stems demonstrated less subsidence and rotation. These studies all suggest that a hydroxyapatite coating enhances the early fixation of the femoral component and has a positive effect in femoral remodelling and in the achievement of a biological fixation between the bone and implant surface.

It can be concluded from this study that a hydroxyapatite coating significantly enhanced bone apposition and ongrowth onto the implant surface when compared with an uncoated porous and grit blasted surface. This is in accordance with the results obtained in the animal studies also reported in this thesis. In these studies bone was observed in direct contact with the HA coating and in chapter two, which is comparable with this study, significantly more bone was observed on surfaces coated with crystalline hydroxyapatite when compared with the uncoated surface. In conclusion, the application of a hydroxyapatite coating is highly advantageous when encouraging bone attachment and ingrowth to the uncemented interface. This enhanced bony response was observed in both animal and human studies. Therefore, a hydroxyapatite coating is an important factor to consider when optimising an uncemented interface in terms of encouraging maximal bone growth at the interface.

CHAPTER SIX

GENERAL DISCUSSION

The hypothesis of this study was that bone ingrowth and attachment could be adapted by the use of bioactive coatings and by engineering implants to produce interfacial strains that lead to beneficial bone remodelling.

The aim of my study was three-fold.

1. To examine and compare bone ingrowth and attachment to extra-cortical plates of different geometric designs and different surface coatings.

2. To investigate whether extra-cortical plates provided a reliable and adequate method for the fixation of massive segmental bone tumour replacements.

3. To investigate osseointegration at the uncemented interface of femoral components retrieved at human autopsy.

Chapter three of my thesis examined bone ingrowth and attachment to extra-cortical plates of different geometric design and surface coating. This study aimed to clarify the conditions necessary to encourage maximal amounts of bone ingrowth and attachment to the plate surface. This study found that only the 'holed' plate design significantly increased bone formation when compared with the control plate ($p=0.01$). A hydroxyapatite coating (with the exception of the solution precipitated coating) had significantly greater interfacial contact with bone when compared to a roughened titanium surface ($p=0.01$). Significantly more bone attached to a crystalline HA coating compared with the HA coating of lower crystallinity ($p=0.004$) although significantly more bone formed in the vicinity of the lower crystalline HA coating ($p=0.036$). Differences in the bony reaction induced by the various geometric designs were evident and I concluded in this study that the optimal plate requires a combination of the correct design and surface coating for maximal bone attachment and ingrowth.

In Chapter 4, a mid shaft segmental tibial replacement was used in the goat model where a 50mm segment of bone was resected and either a 2, 3 or 6 plated implant design was inserted. Implants retrieved 12 months following surgery were all securely fixed by new bone growth. Bone was found to have grown over the ends of the plates and through slots in the plates incorporating the prosthesis into a remodelled cortex. Fluorescein bone markers demonstrated significantly increased bone growth into the slots of the plates ($p<0.05$). Analysis of the second moment of area demonstrated that the 6 plated implant was stiffest and the 2 plated design most flexible. The 2 plated implant was the only design that did not significantly increase the second moment of area of the tibia when implanted ($p=0.235$) although bone remodelling and appeared to create the least amounts of osteoporosis.

In this chapter I concluded that extra-cortical plate fixation is an adequate method when used to fix massive segmental bone tumour prostheses to bone in load-bearing situations. I also concluded that this form of cementless fixation is a reliable alternative to cemented intramedullary stem fixation in these cases.

Indications for the use of extra-cortical plates

These implants have been inserted by Mr Cobb at the Middlesex Hospital and patients show overgrowth of bone adjacent to the plates. Figure 26 in chapter four of my thesis is a photoradiograph of a distal femoral massive prosthesis fixed using extra-cortical plates.

One of the most common problems reported when metal is attached to bone is stress protection osteopenia caused by a mis-match in moduli. Osteopenia was evident in bone beneath plates investigated in both chapter three and four of my thesis. However, due to the success achieved from plate fixation in bone fracture repair and the success obtainable when extra-cortical plates are used to fix massive segmental bone tumour prostheses,

many studies are investigating ways to improve stress protection atrophy associated with plate fixation.

Absorbable plates (α-polyesters or poly (α-hydroxy) acids or tyrosine-derived polycarbonates (Hollinger and Battistone, 1986; Bostman, 1991; Piskin, 1994)) and non-degradable plates of reduced stiffness offer the advantages of a Young's modulus closer to bone thus allowing a more physiological transfer of stresses at the interface. Several studies have reported accelerated healing when less rigid plastic plates were fixed to bone (Brown *et al.* 1980; Ali *et al.* 1990; Pemberton *et al.* 1992). Further studies have investigated plates composed of reinforced polymers (Woo *et al.* 1974; Coutts *et al.* 1976; Tonino *et al.* 1984), carbon-fibre reinforced plates (Akeson *et al.* 1975; Claes *et al.* 1980; Foux *et al.* 1995), polyacetal plates with a metal core (Hutzschenreuter *et al.* 1980) and graphite fibre and methylmethacrylate composite plates (Woo *et al.* 1974). In the future, implants made from these less stiff materials may be considered for the fabrication of prostheses used to treat segmented bone tumours.

From the results obtained in chapter three it was concluded that a crystalline HA coating achieved better bone integration when compared with a HA coating of lower crystallinity, a roughened titanium surface and a solution precipitated HA coating.

The ideal HA coating is one that is stable and slowly resorbs with the ability to achieve rapid union with host bone. However, this results in a decrease in the release of calcium and phosphate from its surface. It is likely that a critical amount of degradation is essential to obtain rapid biological fixation, but premature dissolution of a coating or loss of mechanical bonding to the metal substrate must be avoided (Jaffe and Scott, 1996). *In vivo* studies have demonstrated that higher crystalline HA's degrade less than the more amorphous coatings (van Blitterswijk *et al.* 1993; van Blitterswijk *et al.* 1994). The source of free calcium and phosphorous appears to be the amorphous

calcium phosphate phase and is reported to be present in all hydroxyapatite coatings. The lower crystalline coatings contain more of the amorphous phase compared the higher crystalline coatings. Results obtained in chapter three of my thesis demonstrated severe fragmentation and delamination of HA coatings ~57% crystallinity when compared with the higher crystalline HA coatings. However, significantly increased amounts of bone growth were measured around these plates. My results suggest that a highly crystalline HA coating (>85%) contains enough of the amorphous calcium phosphate phase to encourage rapid fixation of the implant to bone (direct bone contact was observed as early as 25 days post operation) but not enough of this phase to cause severe degradation of the coating.

Chapter three also investigated bone growth and apposition to crystalline HA coated surfaces and compared them with solution precipitated HA coated surfaces formulated and applied by Dr Blumenthal. A solution-deposition process can result in a pure, highly crystalline, thin and firmly adhering HA coating. An advantage in using this process is that a uniform HA layer can be applied to uneven surfaces (eg. porous surfaces). The solution deposited HA coatings are also easy to manufacture, control and apply and may therefore offer distinct advantages over the plasma spray process. In my study and due to the high solubility of the solution precipitated HA coating, significantly less bone contact was seen when compared with plasma sprayed HA. The solubility of this coating can be altered by substituting different negative ions such as the fluoride ion. Therefore, further work is required to clarify the optimal conditions when applying this type of coating and hence determine its true biological potential.

Redepenning *et al.* 1996 investigated electrolytically deposited highly pure brushite coatings ($CaHPO_4 \cdot 2H_2O$) onto titanium substrates. The study concluded that the brushite coating encouraged more bone ingrowth into porous implants when compared with uncoated controls however significantly more bone ingrowth was measured growing into HA coated

porous surfaces when compared with the brushite coatings. A study by Yan *et al.* 1997 applied a dense and uniform apatite layer onto titanium implants using a biomimetic method composed of apatite nucleation and growth steps in simulated body fluid. The study demonstrated a carbonate containing HA to bond directly with both the titanium substrate and bone. Mechanical tests showed interfacial strengths significantly higher than the uncoated controls.

In conclusion, the osteoporotic problems associated with metal plate fixation may be solved through the use of less rigid plates, absorbable plates or through modifications at the plate interface. Changes to plate geometry may also have significant effects as chapter three and four of my thesis demonstrated. Bone turnover increased in regions close to slots in the plates and chapter three showed how most bone ingrowth occurred into a 'holed' design when compared with a control. It is logical to predict that extra-cortical plates of different geometric design would apply different mechanical loads at the plate-bone interface and thus induce more or less bone apposition and ingrowth. However, the elastic modulus of each plate compared in this chapter was not measured and so no conclusions like this can be drawn.

From the results obtained in my thesis and from the short-term results obtained from the few clinical trials and from their use in bone fracture repair, extra-cortical plates have a distinct role in orthopaedics.

The purpose of chapter five was to investigate bone and its response to different surface coatings in the uncemented human situation. The proximal region of each femoral component was coated with one of three different surface types and placed randomly into consenting patients. A plasma sprayed porous ingrowth surface (plain porous) was compared with a hydroxyapatite coated porous surface (porous HA) and a grit blasted surface finish (interlok).

A stable bone-implant interface is critical for the success of an uncemented implant. A stable interface will allow vascular invasion and new bone formation enabling the implant to withstand normal torsonial, bending and axial loads (Cameron *et al.* 1973; Aspenberg *et al.* 1992; Feighan *et al.* 1995; Sandborn *et al.* 1998). In this chapter I reported well-fixed porous-coated human hip retrievals with 23% bone ingrowth into titanium porosities. My results agree with many studies that report bone ingrowth and adequate fixation following uncemented fixation using titanium porous coated implants (Harris *et al.* 1983; Spector *et al.* 1983, Brooker and Collier, 1984; Bobyn and Engh, 1984; Cook *et al.* 1988; Cook[a] *et al.* 1988).

The porous coated implants investigated in my thesis were applied using the plasma-spray process. Histological analysis demonstrated no bead fracture nor delamination of this coating.

The femoral components investigated in Chapter five demonstrated no significant difference in bone attachment to the porous coated surface when compared with the grit blasted surface (Ra 6μm). Histological examination of the grit blasted extra-cortical plates investigated in both chapter three and four demonstrated that in the majority of regions along the implant surface, bone was close to but not in direct contact with the titanium surface.

Grit blasted surfaces have been extensively studied and are considered to have a surface topography that following bone apposition and ingrowth results in a mechanically stable and long-lasting fixation between implant and bone. Wilke *et al.* 1990 measured the torque removal force for implanted screws and found a general trend of increasing removal torque with increasing implant surface roughness. A study by Feighan *et al.* 1995 investigated titanium alloy plugs of different surface roughness (smooth, 0.4μm Ra and 5.0μm Ra). Implants were press fit into the femoral canal of rabbits. They concluded that blasting of the surface of titanium alloy

increased the rate and amount of bone formation onto the surface of the implant and resulted in interfacial pull-out strengths equivalent to those of porous coated implants.

Zweymuller *et al.* 1988 evaluated clinically retrieved, well-fixed roughened titanium alloy hip implants and observed new bone formation directly on the implant as early as 3 weeks after implantation.

HA contributes to an increased implant interfacial strength (Geesink *et al.* 1988), faster bone ingrowth and formation at the bone-implant interface (Denisson *et al.* 1990), filling of interfacial gaps (Overgaard *et al.* 1997), a reduction in interfacial fibrous tissue and protection against metal ion release (Ducheyne and Healy, 1988). The results obtained in chapter five demonstrated the significant effect that a HA coating had on both bone ingrowth (~30%) and attachment (~37%) to the porous HA surface when compared with a plain porous surface ($p=0.012$ (~21%) and $p=<0.05$ (~19%) respectively). The ratio of bone attachment to ingrowth was found to be greater on porous HA than on the plain porous surface with bone forming preferentially along the HA coating when compared with the plain surface. This is indicative of the osseoconductive nature of HA.

Presently, the major concern following the application of a HA coating is its dissolution over time. It is thought that this condition could lead to implant failure (Biesebrock and Edgerton, 1995). Bauer *et al.* 1991, Lintner *et al.* 1994 and Caulier *et al.* 1995 reported results obtained from retrieval studies and all studies observed a reduction in the amount of HA coating on the implant surface. Many theories have been suggested to explain HA degradation at the implant interface. These include phagocytosis by macrophages and resorption by osteoclasts, dissolution at low pH and HA delamination.

Bonding of the hydroxyapatite coating to the substrate is important and is influenced by many factors including the texture of the substrate, the processing conditions and the composition of the coating. Overgaard *et al.* 1998 compared grit blasted HA coated and porous HA coated implants and reported a higher interfacial strength for HA coated porous implants. They concluded that a plasma sprayed porous-coated implant surface seems to give better fixation not only at the HA coating - implant surface but also at the bone - implant surface when compared to HA coated grit blasted surfaces. This has led to the introduction of design variables for example, grooves manufactured onto the implant surface to protect the HA coating (Cook *et al.* 1988).

The potential of HA delamination raises concerns that the subsequent release of HA debris may enter the joint space and thus damage the implant surfaces through third body wear. There is also concern that these particles might stimulate phagocytosis resulting in osteolysis and implant loosening. Bauer[a] *et al.* 1994 used laser profilometry to compare the extent of surface abrasion on modular heads obtained from implants coated with HA with those from cemented and uncemented (porous) without HA. Their results demonstrated increased surface roughness in all groups of modular heads, however cobalt-chrome alloy heads from the HA coated group demonstrated significantly less surface roughness, fewer over all scratches that were not as deep as the heads retrieved from the porous and uncemented group. They concluded from their study that excessive wear was no more of a problem with HA coated components than with cemented or porous implants.

Particles of HA have commonly been identified within histiocytes adjacent to implants. Nevertheless, these cells do not appear to proliferate into the large histiocytic granulomas commonly associated with polyethylene induced osteolysis. HA induced osteolysis has not been a significant problem in the clinical series of HA coated femoral components as has particulate

polyethylene. Wang *et al.* 1994 reported bone formation around cementless implants in the presence of phagocytosable HA particles.

It is reasonable to suspect that if extensive delamination of HA were to occur in the immediate postoperative period before adequate bone remodelling had developed, then perhaps the mechanical stability of the implant component may be compromised. However, the excellent clinical results reported so far for HA coated components suggests that delamination is not a significant problem (D'Antonio *et al.* 1992; Geesink, 1993). Implants, which by their design poorly transmit load, are less likely to maintain their fixation.

Many studies are also investigating ways to further encourage bone attachment and ingrowth to the uncemented implant surface. Bobyn[a] *et al.* 1980 suggested that petaling the bone surface prior to implant insertion increased the implant fixation strength of uncemented porous coated implants. They concluded that the petaling procedure stimulates a greater osteogenic response than mere elevation of the periosteum alone.

Another approach to encourage greater bone ingrowth to the uncemented implant is the application of bone chips or grafts at the interface. Chapter five of my thesis observed residual bone chips at the uncemented interface of hip retrievals and histological analysis revealed how these bone particles appeared to act as a scaffold for the formation of new bone formation adjacent to the implant. In the literature autologous bone chips have been reported to be osseoinductive and osseoconductive (McDonald *et al.* 1988; Bloebaum *et al.* 1992). Allogenic bone chips have also been demonstrated to enhance uncemented implant fixation (Kienapfel *et al.* 1992). However, a study by Chappard *et al.* 1996 investigated xenogenic bone particles at the implant interface and concluded that the bone chips were ineffective at increasing attachment to the implant surface.

Results obtained in chapter five also demonstrated that there was an uneven distribution of bone ingrowth into the plain porous structure with significantly more bone found in the distal region (31%) of the coating than in the proximal (20%). Ingrowth into the HA coated porous regions was more evenly distributed and no significant differences were found at the different levels throughout the porous coating. This uneven distribution of bone was also evident when bone attachment results were quantified. The results also showed how HA encouraged a more even distribution of bone ingrowth and attachment to the proximal region of the femoral stem. This in turn may have significant effects in sealing the bone-implant interface. These effects may be two-fold. Firstly a seal may prevent the migration of wear particles leading to osteolysis and secondly may reduce the effects of stress shielding in the proximal area of bone. A study by Bobyn *et al.* 1995 investigated the tissue response and migration of polyethylene debris at uncemented smooth and porous implant surfaces in the canine model. They reported that the smooth implant surfaces were more susceptible than porous surfaces to the development of a fibrous tissue filled periimplant cavity and the subsequent migration of polyethylene wear debris. They concluded that the relative protection afforded by a porous coating against wear debris migration is a crucial design criterion influencing the longevity of noncemented prostheses. Lord and Bancel, 1983 reported the necessity of a fully porous coated stem to eliminate the presence of smooth surface portions that would allow fibrous encapsulation of the implant. They reported that a fibrous capsule might contribute to increased relative motion between the tip of the stem and the surrounding cortex resulting in pain.

The concept of cementless fixation where the implant is stabilised by the direct attachment of bone is attractive because it may offer a permanent interface. Cement usually induces a fibrous tissue interface, and therefore migration of wear particles can get down the interface. Cement does fatigue over time such that even the most well fixed cemented replacement will eventually fail. The uncemented interface offers the promise of a biological

interface that may remodel and adapt to the needs of its local environment. However, contemporary uncemented implant fixation is not yet perfect. It is well known that the modulus and mechanical properties of metals are different to that of bone and that these differences result in numerous structural alterations (either bone formation or resorption) in the immediate vicinity of the implant. Recent clinical and radiographic studies investigating uncemented implants report increased incidences of thigh pain (Bourne *et al.* 1994) and increased amounts of stress-protected bone resorption (Natarajan *et al.* 1990) when compared with the cemented counterpart. The longevity of uncemented implant fixation as with cemented fixation is also compromised by wear activated osteolysis.

My thesis showed that bone formation and ingrowth occurred into and around extra-cortical plates. The presence of slots or holes in the plate augmented the fixation by providing a larger surface area for bone attachment. My study also showed how a highly crystalline hydroxyapatite coating significantly encouraged both more bone ingrowth and attachment to an extra-cortical plate compared with HA coatings of lower crystallinity, a roughened titanium surface and a solution precipitated hydroxyapatite coating. Based on these results a massive segmental bone tumour animal model was developed where fixation of the implant relied on the osseo-mechanical integration of extra-cortical plates into the cortex of bone. Results showed how the plates altered local stresses in bone such that they appeared to become incorporated into the load bearing structure. All of the implants investigated were fixed by new bone formation and none became loose. Thus osseo-mechanical integration and the highly crystalline hydroxyapatite coated extra-cortical plates resulted in a stable and effective method of fixation in the segmented bone tumour model. This was confirmed in the FEA study performed by Teman, 1998. My study evaluated the effectiveness of highly crystalline HA for uncemented fixation of the femoral stem in the human environment. Results agreed with those obtained

in the previous chapters such that a highly crystalline hydroxyapatite coating significantly encouraged more bone ingrowth and attachment to the uncemented surface.

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                   n Sao Paulo, Brazil - 1976 to 1986
5. 300:0/0.00      $a394 leaves
6. 502:0/0.00      $aThesis: (University of London) 1992
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